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(54) Title: REVERSE-TURN MIMETICS AND METHOD RELATING THERETO

(57) Abstract: Conformationally constrained compounds which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins are disclosed. Such reverse-turn mimetic structures have utility over a wide range of fields, including use as diagnostic and therapeutic agents. Libraries containing the reverse-turn mimetic structures of this invention are also disclosed as well as methods for screening the same to identify biologically active members. The invention also relates to the use of such compounds for inhibiting or treating disorders modulated by Wnt-signaling pathway, such as cancer, especially colorectal cancer, restenosis associated with angioplasty, polycystic kidney disease, aberrant angiogenesis disease, rheumatoid arthritis disease,or ulcerative colitis.

REVERSE-TURN MIMETICS AND METHOD RELATING THERETO

TECHNICAL FIELD

The present invention relates generally to reverse-turn mimetic structures and to a chemical library relating thereto. The invention also relates to applications in the treatment of cancer diseases and pharmaceutical compositions comprising them

BACKGROUND ART

Random screening of molecules for possible activity as therapeutic agents has occurred for many years and resulted in a number of important drug discoveries. While advances in molecular biology and computational chemistry have led to increased interest in what has been termed "rational drug design", such techniques have not proven as fast or reliable as initially predicted. Thus, in recent years there has been a renewed interest and return to random drug screening. To this end, particular strides having been made in new technologies based on the development of combinatorial chemistry libraries, and the screening of such libraries in search for biologically active members.

In general, combinatorial chemistry libraries are simply a collection of molecules. Such libraries vary by the chemical species within the library, as well as the methods employed to both generate the library members and identify which members interact with biological targets of interest. While this field is still young, methods for generating and screening libraries have already become quite diverse and sophisticated. For example, a recent review of various combinatorial chemical libraries has identified a number of such techniques (Dolle, *J. Com. Chem.*, 2(3): 383-433, 2000), including the use of both tagged and untagged library members (Janda, *Proc. Natl. Acad. Sci. USA* 91:10779-10785, 1994).

Initially, combinatorial chemistry libraries were generally limited to members of peptide or nucleotide origin. To this end, the techniques of Houghten et al. illustrate an example of what is termed a "dual-defined iterative" method to assemble soluble combinatorial peptide libraries via split synthesis techniques (*Nature* (London) 354:84-86, 1991; *Biotechniques* 13:412-421, 1992; Bioorg. *Med. Chem. Lett.* 3:405-412, 1993). By this technique, soluble peptide libraries containing tens of millions of members have been obtained. Such libraries have been shown to be effective in the identification of opioid peptides, such as methionine- and leucine-enkephalin (Dooley and Houghten, *Life Sci.* 52, 1509-1517, 1993), and a N-acylated peptide library has been used to identify acetalins, which are potent opioid antagonists (Dooley et al., *Proc. Natl. Acad. Sci. USA* 90:10811-

10815, 1993. More recently, an all D-amino acid opioid peptide library has been constructed and screened for analgesic activity against the mu ("μ ") opioid receptor (Dooley et al, *Science* 266:2019-2022, 1994).

While combinatorial libraries containing members of peptide and nucleotide origin are of significant value, there is still a need in the art for libraries containing members of different origin. For example, traditional peptide libraries to a large extent merely vary the amino acid sequence to generate library members. While it is well recognized that the secondary structures of peptides are important to biological activity, such peptide libraries do not impart a constrained secondary structure to its library members.

To this end, some researchers have cyclized peptides with disulfide bridges in an attempt to provide a more constrained secondary structure (Tumelty et al., *J. Chem. Soc.* 1067-68, 1994; Eichler et al., *Peptide Res.* 7:300-306, 1994). However, such cyclized peptides are generally still quite flexible and are poorly bioavailable, and thus have met with only limited success.

More recently, non-peptide compounds have been developed which more closely mimic the secondary structure of reverse-turns found in biologically active proteins or peptides. For example, U.S. Pat. No. 5,440,013 to Kahn and published PCT WO94/03494, PCT WO01/00210A1, and PCT WO01/16135A2 to Kahn these disclose conformationally constrained, non-peptidic compounds, which mimic the three-dimensional structure of reverse-turns.

While significant advances have been made in the synthesis and identification of conformationally constrained, reverse-turn mimetics, there remains a need in the art for small molecules, which mimic the secondary structure of peptides. There has been also a need in the art for libraries containing such members, as well as techniques for synthesizing and screening the library members against targets of interest, particularly biological targets, to identify bioactive library members. For example U.S. Pat. No. 5,929,237 and its continuation-in-part U.S. Pat. No. 6,013,458 to Kahn also discloses conformationally constrained compounds which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins. The synthesis and identification of conformationally constrained, reverse-turn mimetics and their application to diseases were well reviewed by Obrecht (Advances in Med. Chem., 4, 1-68, 1999).

The present invention also fulfills these needs, and provides further related advantages by providing confomationally constrained compounds which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins.

Wnt signaling pathway regulates a variety of processes including cell growth, oncogenesis, and development (Moon et al., 1997, Trends Genet. 13, 157-162 : Miller et al.,

1999, Oncogene 18, 7860-7872 : Nusse and Varmus, 1992, Cell 69, 1073-1087 : Cadigan and Nusse, 1997, Genes Dev. 11, 3286-3305 : Peifer and Polakis, 2000 Science 287, 1606-1609 : Polakis 2000, Genes Dev. 14, 1837-1851). Wnt signaling pathway has been intensely studied in a variety of organisms. The activation of TCF4/β-catenin mediated transcription by Wnt signal transduction has been found to play a key role in its biological functions (Molenaar et al., 1996, Cell 86, 391-399 : Gat et al., 1998 Cell 95, 605-614 : Orford et al., 1999 J. Cell. Biol. 146, 855-868).

In the absence of Wnt signals, tumor suppressor gene adenomatous polyposis coli (APC) simultaneously interacts with the serine kinase glycogen synthase kinase (GSK)-3β and β-catenin (Su et al., 1993, Science 262, 1734-1737: Yost et al., 1996 Genes Dev. 10, 1443-1454: Hayashi et al., 1997, Proc. Natl. Acad. Sci. USA, 94, 242-247: Sakanaka et al., 1998, Proc. Natl. Acad. Sci. USA, 95, 3020-3023: Sakanaka and William, 1999, J. Biol. Chem 274, 14090-14093). Phosphorylation of APC by GSK-3β regulates the interaction of APC with β-catenin, which in turn may regulate the signaling function of β-catenin (B. Rubinfeld et al., Science 272, 1023, 1996). Wnt signaling stabilizes β-catenin allowing its translocation to the nucleus where it interacts with members of the lymphoid enhancer factor (LEF1)/T-cell factor (TCF4) family of transcription factors (Behrens et al., 1996 Nature 382, 638-642 : Hsu et al., 1998, Mol. Cell. Biol. 18, 4807-4818 : Roose et all., 1999 Science 285, 1923-1926).

Recently c-myc, a known oncogene, was shown to be a target gene for β-catenin/TCF4-mediated transcription (He et al., 1998 Science 281 1509-1512: Kolligs et al., 1999 Mol. Cell. Biol. 19, 5696-5706). Many other important genes, including cyclin D1, and metalloproteinase, which are also involved in oncogenesis, have been identified to be regulated by TCF4/bata-catenin transcriptional pathway (Crawford et al., 1999, Oncogene 18, 2883-2891: Shtutman et al., 1999, Proc. Natl. Acad. Sci. USA., 11, 5522-5527 : Tetsu and McCormick, 1999 Nature, 398, 422-426).

Moreover, overexpression of several downstream mediators of Wnt signaling has been found to regulate apoptosis (Moris et al., 1996, Proc. Natl. Acad. Sci. USA, 93, 7950-7954 : He et al., 1999, Cell 99, 335-345 : Orford et al, 1999 J. Cell. Biol., 146, 855-868: Strovel and Sussman, 1999, Exp. Cell. Res., 253, 637-648). Overexpression of APC in human colorectal cancer cells induced apoptosis (Moris et al., 1996, Proc. Natl. Acad. Sci. USA.,93, 7950-7954), ectopic expression of β-catenin inhibited apoptosis associated with loss of attachment to extracellular matrix (Orford et al, 1999, J. Cell Biol.146, 855-868). Inhibition of TCF4/β-catenin transcription by expression of dominant-negative mutant of TCF4 blocked Wnt-1-mediated cell survival and rendered cells sensitive to apoptotic stimuli such as anti-cancer agent (Shaoqiong Chen et al., 2001, J. Cell. Biol., 152, 1, 87-96) and APC mutation inhibits apoptosis by allowing constitutive survivin expression, a

well-known anti-apoptotic protein (Tao Zhang et al., 2001, Cancer Research, 62, 8664-8667).

Although mutations in the Wnt gene have not been found in human cancer, a mutation in APC or β-catenin, as is the case in the majority of colorectal tumors, results in inappropriate activation of TCF4, overexpression of c-myc and production of neoplastic growth (Bubinfeld et al, 1997, Science, 275, 1790-1792 : Morin et al, 1997, Science, 275, 1787-1790 : Casa et al, 1999, Cell. Growth. Differ. 10, 369-376). The tumor suppressor gene (APC) is lost or inactivated in 85% of colorectal cancers and in a variety of other cancers as well (Kinzler and Vogelstein, 1996, Cell 87, 159-170). APC's principal role is that of a negative regulator of the Wnt signal transduction cascade. A center feature of this pathway involves the modulation of the stability and localization of a cytosolic pool of β-catenin by interaction with a large Axin-based complex that includes APC. This interaction results in phosphorylation of β-catenin thereby targeting it for degradation.

CREB binding proteins (CBP)/p300 were identified initially in protein interaction assays, first through its association with the transcription factor CREB (Chrivia et al, 1993, Nature, 365, 855-859) and later through its interaction with the adenoviral-transforming protein E1A (Stein et al., 1990, J. Viol., 64, 4421-4427 : Eckner et al., 1994, Genes. Dev., 8, 869-884). CBP had a potential to participate in variety of cellular functions including transcriptional coactivator function (Shikama et al., 1997, Trends. Cell. Biol., 7, 230-236 : Janknecht and Hunter, 1996, Nature, 383, 22-23). CBP/p300 potentiates β-catenin-mediated activation of the siamois promoter, a known Wnt target (Hecht et al, 2000, EMBO J. 19, 8, 1839-1850). β-catenin interacts directly with the CREB-binding domain of CBP and β-catenin synergizes with CBP to stimulate the transcriptional activation of TCF4/β-catenin (Ken-Ichi Takemaru and Randall T. Moon, 2000 J. Cell. Biol., 149, 2, 249-254).

From this background, TCF4/β-catenin and CBP complex of Wnt pathway can be taken as target molecules for the regulation of cell growth, oncogenesis and apoptosis of cells, etc. That is, there is a need for compounds that block TCF4/β-catenin transcriptional pathway by inhibiting CBP, and therefore can be used for treatment of cancer, especially colorectal cancer.

BRIFF DESCRIPTION OF THE DRAWING

Fig 1. Shows a graph for the measurement of IC50 of a compound of the present invention for SW480 cells, wherein Cell growth inhibition on SW480 cells is measured at various concentrations of the compound prepared in Example 4 in order to obtain the IC_{50} value. Specifically, the degree of inhibition in firefly and renilla luciferase activities by said test compound was determined. As a result, IC_{50} of said test compound against

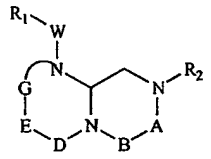
SW480 cell growth was found as disclosed in Table 4. Detailed procedures are the same as disclosed in Example 6.

DISCLOSURE OF THE INVENTION

The present invention is directed to conformationally constrained compounds which mimic the secondary structure of reverse-turn regions of biological peptide and proteins (also referred to herein as "reverse-turn mimetics" and chemical libraries relating thereto. This invention also discloses libraries containing such compounds, as well as the synthesis and screening thereof.

The reverse-turn mimetic structures of the present invention are useful as bioactive agents, including (but not limited to) use as diagnostic, prophylactic and/or therapeutic agents. The reverse-turn mimetic structure libraries of this invention are useful in the identification of such bioactive agents. In the practice of the present invention, the libraries may contain from tens to hundreds to thousands (or greater) of individual reverse-turn structures (also referred to herein as "members").

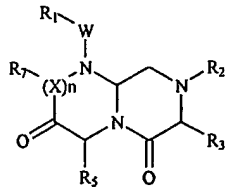
The compounds of the present invention have the following general formula (I):



(I)

wherein A is -(CHR_3)- or -(C=O)-, B is -(CHR_4)- or -(C=O)-, D is –(CHR_5)- or –(C=O)-, E is –(ZR_6)- or -(C=O)-, G is –(XR_7)$_n$-, -(CHR_7)-(NR_8)-, -(C=O)-(XR_9)-, or -(C=O)- , W is –Y(C=O)-, -(C=O)NH-, -(SO_2)- or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers thereof.

In the embodiment wherein A is –(CHR_3)-, B is –(C=O)-, D is –(CHR_5)-, E is –(C=O)-, and G is –(XR_7)$_n$-, the compounds of this invention have the following formula (II):

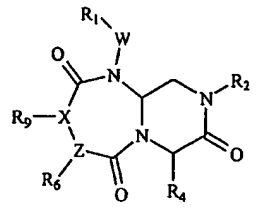


(II)

Wherein W, Y and n are as defined above, and R_1, R_2, R_3, R_5 and R_7 are as defined in the

following detailed description.

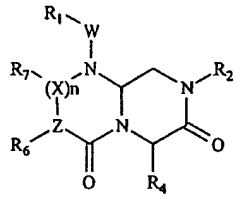
In the embodiment wherein A is –(C=O)-, B is -(CHR_4) -, D is –(C=O)-, E is –(ZR_6)-, and G is –(C=O)-(XR_9)-, the compounds of this invention have the following formula (III):



(III)

wherein W, Y and n are as defined above, Z is nitrogen or CH (when Z is CH, then X is nitrogen), and R_1, R_2, R_4, R_6 and R_9 are as defined in the following detailed description.

In the embodiment wherein A is –(C=O)-, B is –(CHR_4)-, D is –(C=O)-, E is –(ZR_6)-, and G is (XR_7)$_n$-, the compounds of this invention have the following general formula (IV):



(IV)

wherein W, Y and n are as defined above, Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero), and R_1, R_2, R_4, R_6 and R_7, are as defined in the following detailed description.

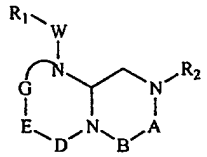
The present invention is also directed to libraries containing compounds of formula (I) above, as well as methods for synthesizing such libraries and methods for screening the same to identify biologically active compounds. Compositions containing a compound of this invention in combination with a pharmaceutically acceptable carrier or diluent are also disclosed.

Especially, the present invention relates pharmaceutical compositions containing thereof for treating disorders including cancers which are associated with Wnt signaling pathway. It further relates to methods for treating disorders including cancer which are associated with Wnt signaling pathway.

These and other aspects of this invention will be apparent upon reference to the attached figures and following detailed description. To this end, various references are set forth herein, which describe in more detail certain procedures, compounds and/or compositions, and are incorporated by reference in their entirety.

In below, the present invention is illustrated in detail.

In one aspect of the present invention, a reverse-turn mimetic structure is disclosed having the following formula (I):



(I)

wherein A is -(CHR_3)- or -(C=O)-, B is -(CHR_4)- or -(C=O)-, D is –(CHR_5)- or –(C=O)-, E is –(ZR_6)- or -(C=O)-, G is –(XR_7)$_n$-, -(CHR_7)-(NR_8)-, -(C=O)-(XR_9)-, or -(C=O)- , W is –Y(C=O)-, -(C=O)NH- , -(SO_2)- or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers thereof.

More specifically, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are independently selected from the group consisting of aminoC_{2-5}alkyl, guanidineC_{2-5}alkyl, C_{1-4}alkylguanidinoC_{2-5}alkyl, diC_{1-4}alkylguanidino-C_{2-5}alkyl, amidinoC_{2-5}alkyl,C_{1-4}alkylamidinoC_{2-5}alkyl, diC_{1-4}alkylamidinoC_{2-5}alkyl, C_{1-3}alkoxy, Phenyl, substituted phenyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), naphthyl, substituted naphthyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridyl, substituted pyridyl, (where the substituents are independently selected from one or more of amino amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridylC_{1-4}alkyl, substituted pyridylC_{1-4}alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano,

sulfuryl or hydroxyl), pyrimidylC_{1-4}alkyl, substituted pyrimidylC_{1-4}alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), triazin-2-yl-C_{1-4}alkyl, substituted triazin-2-yl-C_{1-4}alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), imidazoC_{1-4}alkyl, substituted imidazol C_{1-4}alkl (where the imidazole sustituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), imidazolinylC_{1-4}alkyl, N-amidinopiperazinyl-N-C_{0-4}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, C_{1-5}dialkylaminoC_{2-5}alkyl, N-amidinopiperidinylC_{1-4}alkyl and 4-aminocyclohexylC_{0-2}alkyl.

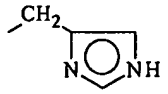
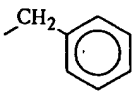
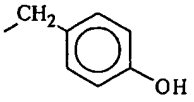
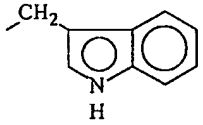
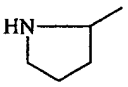
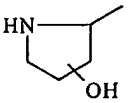
In one embodiment, R_1, R_2, R_6 of E, and R_7, R_8 and R_9 of G are the same or different and represent the remainder of the compound, and R_3 of A, R_4 of B or R_5 of D is selected from an amino acid side chain moiety or derivative thereof. As used herein, the term "remainder of the compound" means any moiety, agent, compound, support, molecule, linker, amino acid, peptide or protein covalently attached to the reverse-turn mimetic structure at R_1, R_2, R_5, R_6, R_7, R_8 and/or R_9 positions. This term also includes amino acid side chain moieties and derivatives thereof.

As used herein, the term "amino acid side chain moiety" represents any amino acid side chain moiety present in naturally occurring proteins including (but not limited to) the naturally occurring amino acid side chain moieties identified in Table 1. Other naturally occurring amino acid side chain moieties of this invention include (but are not limited to) the side chain moieties of 3,5-dibromotyrosine, 3,5-diiodotyrosine, hydroxylysine, γ-carboxyglutamate, phosphotyrosine and phosphoserine. In addition, glycosylated amino acid side chains may also be used in the practice of this invention, including (but not limited to) glycosylated threonine, serine and asparagine.

TABLE 1

Amino Acid Side Chain Moieties

Amino Acid Side Chain Moiety	Amino Acid
–H	Glycine
$–CH_3$	Alanine
$–CH(CH_3)_2$	Valine

$-CH_2\,CH(CH_3)_2$	Leucine
$-CH(CH_3)CH_2\,CH_3$	Isoleucine
$-(CH_2)_4NH_3^+$	Lysine
$-(CH_2)_3NHC(NH_2)NH_2^+$	Arginine
	Histidine
$-CH_2COO^-$	Aspartic acid
$-CH_2CH_2COO^-$	Glutamic acid
$-CH_2CONH_2$	Asparagine
$-CH_2CH_2CONH_2$	Glutamine
	Phenylalanine
	Tyrosine
	Tryptophan
$-CH_2SH$	Cysteine
$-CH_2CH_2SCH_3$	Methionine
$-CH_2OH$	Serine
$-CH(OH)CH_3$	Threonine
	Proline
	Hydroxyproline

In addition to naturally occurring amino acid side chain moieties, the amino acid side chain moieties of the present invention also include various derivatives thereof. As used herein, a "derivative" of an amino acid side chain moiety includes modifications and/or variations to naturally occurring amino acid side chain moieties. For example, the

amino acid side chain moieties of alanine, valine, leucine, isoleucine and phenylalanine may generally be classified as lower chain alkyl, aryl, or arylalkyl moieties. Derivatives of amino acid side chain moieties include other straight chain or branched, cyclic or noncyclic, substituted or unsubstituted, saturated or unsaturated lower chain alkyl, aryl or arylalkyl moieties.

As used herein, "lower chain alkyl moieties" contain from 1-12 carbon atoms, "lower chain aryl moieties" contain from 6-12 carbon atoms and "lower chain aralkyl moieties" contain from 7-12 carbon atoms. Thus, in one embodiment, the amino acid side chain derivative is selected from a C_{1-12} alkyl, a C_{6-12} aryl and a C_{7-12} arylalkyl, and in a more preferred embodiment, from a C_{1-7} alkyl, a C_{6-10} aryl and a C_{7-11} arylalkyl.

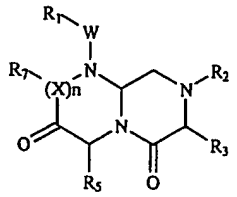
Amino side chain derivatives of this invention further include substituted derivatives of lower chain alkyl, aryl, and arylalkyl moieties, wherein the substituent is selected from (but are not limited to) one or more of the following chemical moieties: -OH, -OR, -COOH, -COOR, -$CONH_2$, -NH_2, -NHR, -NRR, -SH, -SR, -SO_2R, -SO_2H, -SOR and halogen (including F, Cl, Br and I), wherein each occurrence of R is independently selected from straight chain or branched, cyclic or noncyclic, substituted or unsubstituted, saturated or unsaturated lower chain alkyl, aryl and aralkyl moieties. Moreover, cyclic lower chain alkyl, aryl and arylalkyl moieties of this invention include naphthalene, as well as heterocyclic compounds such as thiophene, pyrrole, furan, imidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, pyridine, pyrimidine, purine, quinoline, isoquinoline and carbazole. Amino acid side chain derivatives further include heteroalkyl derivatives of the alkyl portion of the lower chain alkyl and aralkyl moieties, including (but not limited to) alkyl and aralkyl phosphonates and silanes.

Representative R_1, R_2, R_5, R_6, R_7, R_8 and R_9 moieties specifically include (but are not limited to) -OH, -OR, -COR, -COOR, -$CONH_2$, -CONR, -CONRR, -NH_2, -NHR, -NRR, -SO_2R and -COSR, wherein each occurrence of R is as defined above.

In a further embodiment, and in addition to being an amino acid side chain moiety or derivative thereof (or the remainder of the compound in the case of R_1, R_2, R_5, R_6, R_7, R_8 and R_9), R_1, R_2, R_5, R_6, R_7, R_8 or R_9may be a linker facilitating the linkage of the compound to another moiety or compound. For example, the compounds of this invention may be linked to one or more known compounds, such as biotin, for use in diagnostic or screening assay. Furthermore, R_1, R_2, R_5, R_6, R_7, R_8 or R_9 may be a linker joining the compound to a solid support (such as a support used in solid phase peptide synthesis) or alternatively, may be the support itself. In this embodiment, linkage to another moiety or compound, or to a solid support, is preferable at the R_1, R_2, R_7 or R_8 position, and more preferably at the R_1 or R_2 position.

In the embodiment wherein A is –(CHR_3)-, B is –(C=O)-, D is –(CHR_5)-, E is –

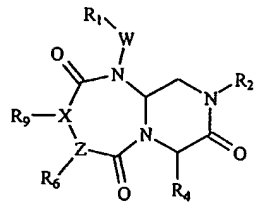
(C=O)-, G is $-(XR_7)_n-$, the reverse turn mimetic compound of this invention have the following formula (II):



(II)

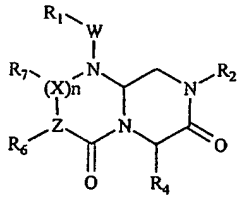
wherein R_1, R_2, R_3, R_5, R_7, W, X and n are as defined above. In a preferred embodiment, R_1, R_2 and R_7 represent the remainder of the compound, and R_3 or R_5 is selected from an amino acid side chain moiety.

In the embodiment wherein A is –(C=O)-, B is -(CHR_4) -, D is –(C=O)-, E is –(ZR_6)-, G is –(C=O)-(XR_9)-, the reverse turn mimetic compound of this invention have the following general formula (III):



(III)

wherein R_1, R_2, R_4, R_6, R_9, W and X are as defined above, Z is nitrogen or CH (when Z is CH, then X is nitrogen). In a preferred embodiment, R_1, R_2 , R_6 and R_9 represent the remainder of the compound, and R_4 is selected from an amino acid side chain moiety. In a more specific embodiment wherein A is –(C=O)-, B is –(CHR_4)-, D is –(C=O)-, E is –(ZR_6)-, G is $(XR_7)_n-$, the reverse turn mimetic compound of this invention have the following formula (IV):



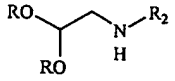
(IV)

wherein R_1, R_2, R_4, R_6, R_7, W, X and n are as defined above, and Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero). In a preferred embodiment, R_1, R_2, R_6 and R_7 represent the remainder of the compound, and R_4 is selected from an amino acid side chain moiety. In this case, R_6 or R_7 may be selected from an amino acid side chain moiety when Z and X are CH, respectively.

The reverse-turn mimetic structures of the present invention may be prepared by

utilizing appropriate starting component molecules (hereinafter referred to as "component pieces"). Briefly, in the synthesis of reverse-turn mimetic structures having formula (II), first and second component pieces are coupled to form a combined first-second intermediate, if necessary, third and/or fourth component pieces are coupled to form a combined third-fourth intermediate (or, if commercially available, a single third intermediate may be used), the combined first-second intermediate and third-fourth intermediate (or third intermediate) are then coupled to provide a first-second-third-fourth intermediate (or first-second-third intermediate) which is cyclized to yield the reverse-turn mimetic structures of this invention. Alternatively, the reverse-turn mimetic structures of formula (II) may be prepared by sequential coupling of the individual component pieces either stepwise in solution or by solid phase synthesis as commonly practiced in solid phase peptide synthesis.

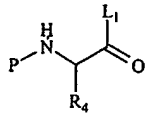
Within the context of the present invention, a "first component piece" has the following formula S1:



(S1)

wherein R_2 as defined above, and R is a protective group suitable for use in peptide synthesis. Suitable R groups include alkyl groups and, in a preferred embodiment, R is a methyl group. Such first component pieces may be readily synthesized by reductive amination or substitution reaction by displacement of H_2N-R_2 from $CH(OR)_2$-CHO or $CH(OR)_2$-CH_2-Hal (wherein Hal means a halogen atom).

A "second component piece" of this invention has the following formula S2:



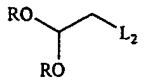
(S2)

where L_1 is carboxyl-activation group such as halogen atom, R_4 is as defined above, and P is an amino protective group suitable for use in peptide synthesis. Preferred protective groups include t-butyl dimethylsilyl (TBDMS), t-Butyloxycarbonyl (BOC), Methyloxycarbonyl (MOC), 9H-Fluorenylmethyloxycarbonyl (FMOC), and allyloxycarbonyl (Alloc). When L is –C(O)NHR, -NHR may be an carboxyl protective group. N-Protected amino acids are commercially available. For example, FMOC amino acids are available from a variety of sources. The conversion of these compounds to the second component pieces of this invention may be readily achieved by activation of the carboxylic acid group of the N-protected amino acid. Suitable activated carboxylic acid groups include acid halides where X is a halide such as chloride or bromide, acid

anhydrides where X is an acyl group such as acetyl, reactive esters such as an N-hydroxysuccinimide esters and pentafluorophenyl esters, and other activated intermediates such as the active intermediate formed in a coupling reaction using a carbodiimide such as dicyclohexylcarbodiimide (DCC).

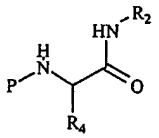
In the case of the azido derivative of an amino acid serving as the second component piece, such compounds may be prepared from the corresponding amino acid by the reaction disclosed by Zaloom et al. (*J. Org. Chem.* 46:5173-76, 1981).

Alternatively, the first piece of the invention may have the following formula S1':



(S1')

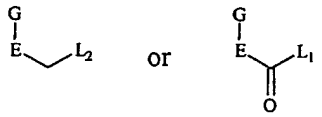
wherein R is as defined above and L_2 is a leaving group such as halogen atom or tosyl group, and the second piece of the invention may have the following formula S2':



(S2')

wherein R_2, R_3 and P are as defined above,

A "third component piece" of this invention has the following formula S3a or S3b:

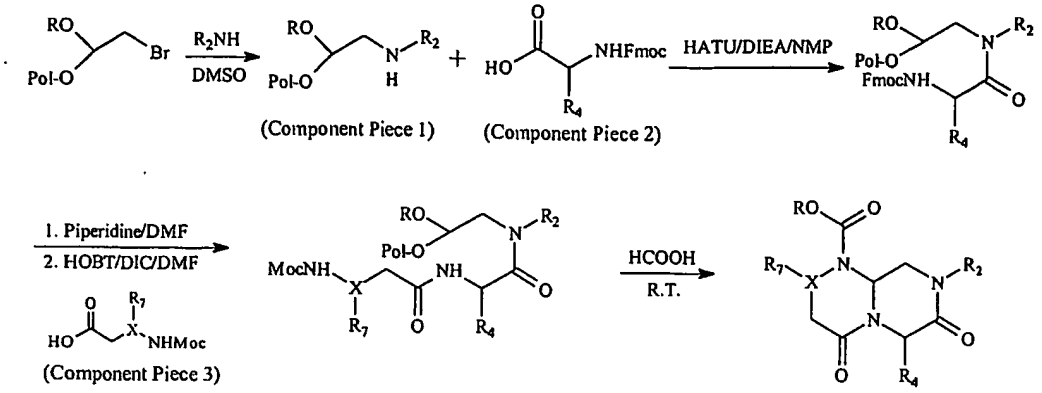


(S3a) (S3b)

where G, E, L_1 and L_2 are as defined above. Suitable third component pieces are commercially available from a variety of sources or can be prepared by any known method in organic chemistry.

More specifically, the reverse-turn mimetic structures of this invention of formula (II) are synthesized by reacting a first component piece with a second component piece to yield a combined first-second intermediate, followed by either reacting the combined first-second intermediate with third component pieces sequentially to provide a combined first-second-third-fourth intermediate, and then cyclizing this intermediate to yield the reverse-turn mimetic structure.

The general synthesis of a reverse-turn having structure I' may be synthesized by the following technique. A first component piece 1 is coupled with a second component piece 2 by using coupling reagent such as phosgene to yield, after N-deprotection, a combined first-second intermediate 1-2 as illustrated below:



wherein, R, R_2, R_4, R_7, Fmoc, Moc and X are as defined above, and Pol represents a polymeric support.

The syntheses of representative component pieces of this invention are described in Preparation Examples and working Examples.

The reverse-turn mimetic structures of formula (III) and (IV) may be made by techniques analogous to the modular component synthesis disclosed above, but with appropriate modifications to the component pieces.

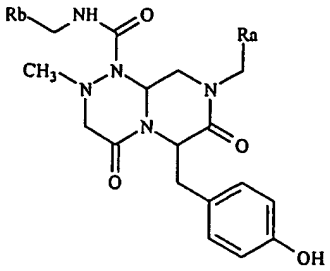
As mentioned above, the reverse-turn mimetics of USP 6,013,458 to Kahn, et al. are useful as bioactive agents, such as diagnostic, prophylactic, and therapeutic agents. The opiate receptor binding activity of representative reverse-turn mimetics is presented in Example 9 of said USP 6,013,458, wherein the reverse-turn mimetics of this invention were found to effectively inhibit the binding of a radiolabeled enkephalin derivative to the δ and μ opiate receptors, of which data demonstrates the utility of these reverse-turn mimetics as receptor agonists and as potential analgesic agents.

The reverse-turn mimetic structures of the present invention will be useful as bioactive agents, such as diagnostic, prophylactic, and therapeutic agents.

Therefore, since the compounds according to the present invention are of reverse-turn mimetic structures, it may be useful for modulating a cell signaling transcription factor related peptides in a warm-blooded animal, comprising administering to the animal an effective amount of the compound of formula (I).

Further, the reverse-turn mimetic structures of the present invention may also be effective for inhibiting peptide binding to PTB domains in a warm-blooded animal; for modulating G protein coupled receptor (GPCR) and ion channel in a warm-blooded animal; for modulating cytokines in a warm-blooded animal.

Meanwhile, it has been found that the compounds of the formula (I), especially compounds of formula (VI) are effective for inhibiting or treating disorders modulated by Wnt-signaling pathway, such as cancer, especially colorectal cancer.



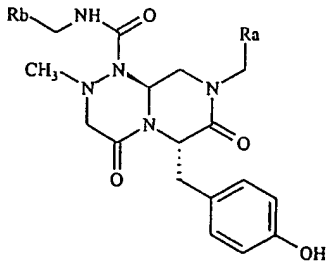
(VI)

wherein, R_a is a bicyclic aryl group having 8 to 11 ring members, which may have 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur, and R_b is a monocyclic aryl group having 5 to 7 ring members, which may have 1 to 2 heteroatoms selected from nitrogen, oxygen or sulfur, and aryl ring in the compound may have one or more substituents selected from a group consisting of halide, hydroxy, cyano, lower alkyl, and lower alkoxy group.

Therefore, it is an object of the present invention to provide a pharmaceutical composition comprising a safe and effective amount of the compound having general formula (VI) and pharmaceutically acceptable carrier, which can be used for treatment of disorders modulated by Wnt signaling pathway, especially by TCF4- β-catenin- CBP complex.

Further, the present invention is to provide a method for inhibiting the growth of tumor cells by using the above-described composition of the present invention; a method for inducing apoptosis of tumor cells by using the above-described composition of the present invention; a method for treating a disorder modulated by TCF4-β catenin-CBP complex by using the above-described composition of the present invention; and a method of treating cancer such as colorectal cancer by administering the composition of the present invention together with other anti-cancer agent such as 5-fluorouracil (5-FU), taxol, cisplatin, mitomycin C, tegafur, raltitrexed, capecitabine, and irinotecan, etc.

In a preferred embodiment of the present invention, the compound of the present invention has a (6S,10R)-configuration as follows:



(VIa)

wherein R_a and R_b have the same meanings as defined above.

In another aspect of this invention, libraries containing reverse-turn mimetic

structures of the present invention are disclosed. Once assembled, the libraries of the present invention may be screened to identify individual members having bioactivity. Such screening of the libraries for bioactive members may involve; for example, evaluating the binding activity of the members of the library or evaluating the effect the library members have on a functional assay. Screening is normally accomplished by contacting the library members (or a subset of library members) with a target of interest, such as, for example, an antibody, enzyme, receptor or cell line. Library members, which are capable of interacting with the target of interest, are referred to herein as "bioactive library members" or "bioactive mimetics". For example, a bioactive mimetic may be a library member which is capable of binding to an antibody or receptor, which is capable of inhibiting an enzyme, or which is capable of eliciting or antagonizing a functional response associated, for example, with a cell line. In other words, the screening of the libraries of the present invention determines which library members are capable of interacting with one or more biological targets of interest. Furthermore, when interaction does occur, the bioactive mimetic (or mimetics) may then be identified from the library members. The identification of a single (or limited number) of bioactive mimetic(s) from the library yields reverse-turn mimetic structures which are themselves biologically active, and thus useful as diagnostic, prophylactic or therapeutic agents, and may further be used to significantly advance identification of lead compounds in these fields.

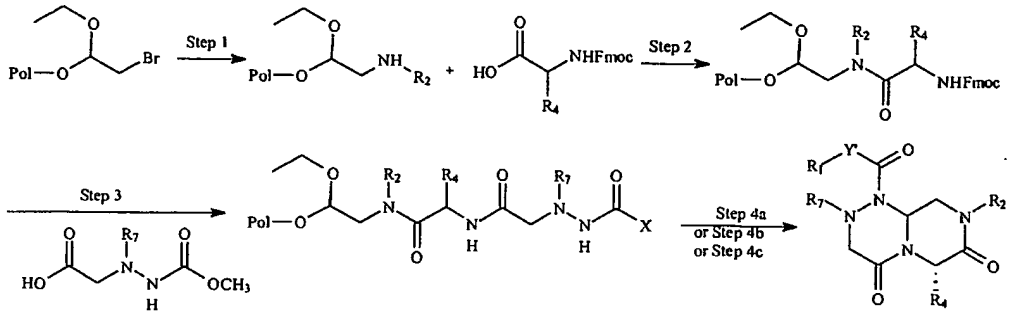
Synthesis of the peptide mimetics of the library of the present invention may be accomplished using known peptide synthesis techniques, in combination with the first, second and third component pieces of this invention. More specifically, any amino acid sequence may be added to the N-terminal and/or C-terminal of the conformationally constrained reverse-turn mimetic. To this end, the mimetics may be synthesized on a solid support (such as PAM resin) by known techniques (see, e.g., John M. Stewart and Janis D. Young, Solid Phase Peptide Synthesis, 1984, Pierce Chemical Comp., Rockford, Ill.) or on a silyl-linked resin by alcohol attachment (see Randolph et al., *J. Am Chem. Soc.* 117:5712-14, 1995).

In addition, a combination of both solution and solid phase synthesis techniques may be utilized to synthesize the peptide mimetics of this invention. For example, a solid support may be utilized to synthesize the linear peptide sequence up to the point that the conformationally constrained reverse-turn is added to the sequence. A suitable conformationally constrained reverse-turn mimetic structures which has been previously synthesized by solution synthesis techniques may then be added as the next "amino acid" to the solid phase synthesis (i.e., the conformationally constrained reverse-turn mimetic, which has both an N-terminus and a C-terminus, may be utilized as the next amino acid to

be added to the linear peptide). Upon incorporation of the conformationally constrained reverse-turn mimetic structures into the sequence, additional amino acids may then be added to complete the peptide bound to the solid support. Alternatively, the linear N-terminus and C-terminus protected peptide sequences may be synthesized on a solid support, removed from the support, and then coupled to the conformationally constrained reverse-turn mimetic structures in solution using known solution coupling techniques.

In another aspect of this invention, methods for constructing the libraries are disclosed. Traditional combinatorial chemistry techniques (see, e.g., Gallop et al., *J. Med. Chem.* 37:1233-1251, 1994) permit a vast number of compounds to be rapidly prepared by the sequential combination of reagents to a basic molecular scaffold. Combinatorial techniques have been used to construct peptide libraries derived from the naturally occurring amino acids. For example, by taking 20 mixtures of 20 suitably protected and different amino acids and coupling each with one of the 20 amino acids, a library of 400 (i.e., 20^2) dipeptides is created. Repeating the procedure seven times results in the preparation of a peptide library comprised of about 26 billion (i.e., 20^8) octapeptides.

Specifically, synthesis of the peptide mimetics of the library of the present invention may be accomplished using known peptide synthesis techniques, for example, the General Scheme of [4,4,0] Reverse-Turn Mimetic Library as follows:



Synthesis of the peptide mimetics of the libraries of the present invention was accomplished using a FlexChem Reactor Block which has 96 well plates by known techniques. In the above scheme 'Pol' represents a bromoacetal resin (Advanced ChemTech) and detailed procedure is illustrated below.

Step 1

A bromoacetal resin (37mg, 0.98 mmol/g) and a solution of R_2-amine in DMSO (1.4mL) were placed in a Robbins block (FlexChem) having 96 well plates. The reaction mixture was shaken at 60℃ using a rotating oven [Robbins Scientific] for 12 hours. The resin was washed with DMF, MeOH, and then DCM

Step 2

A solution of commercial available FmocAmino Acids (4 equiv.), PyBob (4 equiv.), HOAt (4 equiv.), and DIEA (12 equiv.) in DMF was added to the resin. After the reaction mixture was shaken for 12 hours at room temperature, the resin was washed with DMF, MeOH, and then DCM.

Step 3

To the resin swollen by DMF before reaction was added 25% piperidine in DMF and the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and the resin was washed with DMF, Methanol, and then DCM. A solution of hydrazine acid (4 equiv.), HOBt (4 equiv.), and DIC (4 equiv.) in DMF was added to the resin and the reaction mixture was shaken for 12 hours at room temperature. The resin was washed with DMF, MeOH, and then DCM.

Step 4a (Where hydrazine acid is MOC carbamate)

The resin obtained in Step 3 was treated with formic acid (1.2 mL each well) for 18 hours at room temperature. After the resin was removed by filtration, the filtrate was condensed under a reduced pressure using SpeedVac [SAVANT] to give the product as oil. The product was diluted with 50% water/acetonitrile and then lyophilized after freezing.

Step 4b (Where Fmoc hydrazine acid is used to make Urea through isocynate)

To the resin swollen by DMF before reaction was added 25% piperidine in DMF and the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and the resin was washed with DMF, Methanol, then DCM. To the resin swollen by DCM before reaction was added isocynate (5 equiv.) in DCM. After the reaction mixture was shaken for 12 hours at room temperature the resin was washed with DMF, MeOH, then DCM. The resin was treated with formic acid (1.2 mL each well) for 18 hours at room temperature. After the resin was removed by filtration, the filtrate was condensed under a reduced pressure using SpeedVac [SAVANT] to give the product as oil. The product was diluted with 50% water/acetonitrile and then lyophilized after freezing.

Step 4c (Where Fmoc-hydrazine acid is used to make Urea through active carbamate)

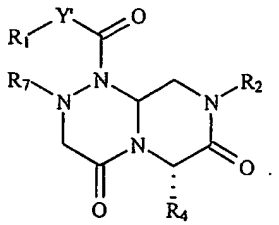
To the resin swollen by DMF before reaction was added 25% piperidine in DMF and the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and the resin was washed with DMF, MeOH, and then DCM.

To the resin swollen by DCM before reaction was added p-nitrophenyl chloroformate (5 equiv.) and diisopropyl ethylamine (5 equiv.) in DCM. After the reaction mixture was shaken for 12 hours at room temperature, the resin was washed with DMF, MeOH, and then DCM. To the resin was added primary amines in DCM for 12 hours at room temperature and the resin was washed with DMF, MeOH, and then DCM. After reaction the resin was treated with formic acid (1.2 mL each well) for 18 hours at room temperature. After the resin was removed by filtration, the filtrate was condensed under a reduced pressure using SpeedVac [SAVANT] to give the product as oil. The product was diluted with 50% water/acetonitrile and then lyophilized after freezing.

To generate these block libraries the key intermediate hydrazine acids were synthesized according to the procedure illustrated in Preparation Examples.

Table 2 shows a [4,4,0] Reverse turn mimetics library which can be prepared according to the present invention, of which representative preparation is given in Example 4

[Table 2] The [4,4,0]Reverse turn mimetics library



No	R_1	R_4	R_7	R_1-Y'	Mol. Weight	M+H
1	2,4-Cl_2-benzyl	4-HO-benzyl	Allyl	OCH_3	533	534
2	2,4-Cl_2-benzyl	4-NO_2-benzyl	Allyl	OCH_3	562	563
3	2,4-Cl_2-benzyl	2,4-F_2-benzyl	Allyl	OCH_3	553	554
4	2,4-Cl_2-benzyl	4-Cl-benzyl	Allyl	OCH_3	552	553
5	2,4-Cl_2-benzyl	2,2-bisphenylethyl	Allyl	OCH_3	594	595
6	2,4-Cl_2-benzyl	3-t-Bu-4-HO-benzyl	Allyl	OCH_3	590	591
7	2,4-Cl_2-benzyl	4-Me-benzyl	Allyl	OCH_3	531	532
8	2,4-Cl_2-benzyl	Cyclohexylmethyl	Allyl	OCH_3	523	524
9	2,4-Cl_2-benzyl	4-F-benzyl	Allyl	OCH_3	535	536
10	2,4-Cl_2-benzyl	2-Cl-benzyl	Allyl	OCH_3	552	553
11	2,4-Cl_2-benzyl	2,4-Cl_2-benzyl	Allyl	OCH_3	586	587
12	2,4-Cl_2-benzyl	Naphth-2-ylmethyl	Allyl	OCH_3	567	568
13	2,4-Cl_2-benzyl	4-HO-benzyl	Benzyl	OCH_3	583	584
14	2,4-Cl_2-benzyl	4-NO_2-benzyl	Benzyl	OCH_3	612	613
15	2,4-Cl_2-benzyl	2,4-F_2-benzyl	Benzyl	OCH_3	603	604
16	2,4-Cl_2-benzyl	4-Cl-benzyl	Benzyl	OCH_3	602	603
17	2,4-Cl_2-benzyl	2,2-bisphenylethyl	Benzyl	OCH_3	644	645
18	2,4-Cl_2-benzyl	3-t-Bu-4-HO-benzyl	Benzyl	OCH_3	640	641
19	2,4-Cl_2-benzyl	4-Me-benzyl	Benzyl	OCH_3	582	583
20	2,4-Cl_2-benzyl	Cyclohexylmethyl	Benzyl	OCH_3	574	575
21	2,4-Cl_2-benzyl	4-F-benzyl	Benzyl	OCH_3	585	586
22	2,4-Cl_2-benzyl	2-Cl-benzyl	Benzyl	OCH_3	602	603
23	2,4-Cl_2-benzyl	2,4-Cl_2-benzyl	Benzyl	OCH_3	636	637

24	2,4-Cl_2-benzyl	Naphth-2-ylmethyl	Benzyl	OCH_3	618	619
25	2,4-Cl_2-benzyl	4-HO-benzyl	Allyl	OCH_3	479	480
26	2,4-Cl_2-benzyl	4-NO_2-benzyl	Allyl	OCH_3	508	509
27	2,4-Cl_2-benzyl	2,4-F_2-benzyl	Allyl	OCH_3	499	500
28	2,4-Cl_2-benzyl	4-Cl-benzyl	Allyl	OCH_3	497	498
29	Phenethyl	2,2-bisphenylethyl	Allyl	OCH_3	539	540
30	Phenethyl	3-t-Bu-4-HO-benzyl	Allyl	OCH_3	535	536
31	Phenethyl	4-Me-benzyl	Allyl	OCH_3	477	478
32	Phenethyl	Cyclohexylmethyl	Allyl	OCH_3	469	470
33	Phenethyl	4-F-benzyl	Allyl	OCH_3	481	482
34	Phenethyl	2-Cl-benzyl	Allyl	OCH_3	497	498
35	Phenethyl	2,4-Cl_2-benzyl	Allyl	OCH_3	531	532
36	Phenethyl	Naphth-2-ylmethyl	Allyl	OCH_3	513	514
37	Phenethyl	4-HO-benzyl	Benzyl	OCH_3	529	530
38	Phenethyl	4-NO_2-benzyl	Benzyl	OCH_3	558	559
39	Phenethyl	2,4-F_2-benzyl	Benzyl	OCH_3	549	550
40	Phenethyl	4-Cl-benzyl	Benzyl	OCH_3	547	548
41	Phenethyl	2,2-bisphenylethyl	Benzyl	OCH_3	589	590
42	Phenethyl	3-t-Bu-4-HO-benzyl	Benzyl	OCH_3	585	586
43	Phenethyl	4-Me-benzyl	Benzyl	OCH_3	527	528
44	Phenethyl	Cyclohexyl-methyl	Benzyl	OCH_3	519	520
45	Phenethyl	4-F-benzyl	Benzyl	OCH_3	531	532
46	Phenethyl	2-Cl-benzyl	Benzyl	OCH_3	547	548
47	Phenethyl	2,4-Cl_2-benzyl	Benzyl	OCH_3	582	583
48	Phenethyl	Naphth-2-ylmethyl	Benzyl	OCH_3	563	564
49	Phenethyl	4-HO-benzyl	Allyl	OCH_3	497	498
50	Phenethyl	4-NO_2-benzyl	Allyl	OCH_3	526	527
51	Phenethyl	2,4-F_2-benzyl	Allyl	OCH_3	517	518
52	Phenethyl	4-Cl-benzyl	Allyl	OCH_3	515	516
53	4-F-phenylethyl	2,2-bisphenylethyl	Allyl	OCH_3	557	558
54	4-F-phenylethyl	3-t-Bu-4-HO-benzyl	Allyl	OCH_3	553	554
55	4-F-phenylethyl	4-Me-benzyl	Allyl	OCH_3	495	496
56	4-F-phenylethyl	Cyclohexyl-methyl	Allyl	OCH_3	487	488
57	4-F-phenylethyl	4-F-benzyl	Allyl	OCH_3	499	500
58	4-F-phenylethyl	2-Cl-benzyl	Allyl	OCH_3	515	516
59	4-F-phenylethyl	2,4-Cl_2-benzyl	Allyl	OCH_3	549	550
60	4-F-phenylethyl	Naphth-2-ylmethyl	Allyl	OCH_3	531	532
61	4-F-phenylethyl	4-HO-benzyl	Benzyl	OCH_3	547	548
62	4-F-phenylethyl	4-NO_2-benzyl	Benzyl	OCH_3	576	577
63	4-F-phenylethyl	2,4-F_2-benzyl	Benzyl	OCH_3	567	568
64	4-F-phenylethyl	4-Cl-benzyl	Benzyl	OCH_3	565	566
65	4-F-phenylethyl	2,2-bisphenylethyl	Benzyl	OCH_3	607	608
66	4-F-phenylethyl	3-t-Bu-4-HO-benzyl	Benzyl	OCH_3	603	604
67	4-F-phenylethyl	4-Me-benzyl	Benzyl	OCH_3	545	546
68	4-F-phenylethyl	Cyclohexyl-methyl	Benzyl	OCH_3	537	538
69	4-F-phenylethyl	4-F-benzyl	Benzyl	OCH_3	549	550
70	4-F-phenylethyl	2-Cl-benzyl	Benzyl	OCH_3	565	566
71	4-F-phenylethyl	2,4-Cl_2-benzyl	Benzyl	OCH_3	599	600
72	4-F-phenylethyl	Naphth-2-ylmethyl	Benzyl	OCH_3	581	582
73	4-F-phenylethyl	4-HO-benzyl	Allyl	OCH_3	509	510
74	4-F-phenylethyl	4-NO_2-benzyl	Allyl	OCH_3	538	539
75	4-F-phenylethyl	2,4-F_2-benzyl	Allyl	OCH_3	529	530
76	4-F-phenylethyl	4-Cl-benzyl	Allyl	OCH_3	527	528
77	4-MeO-phenylethyl	2,2-bisphenylethyl	Allyl	OCH_3	569	570
78	4-MeO-phenylethyl	3-t-Bu-4-HO-benzyl	Allyl	OCH_3	565	566
79	4-MeO-phenylethyl	4-Me-benzyl	Allyl	OCH_3	507	508
80	4-MeO-phenylethyl	Cyclohexyl-methyl	Allyl	OCH_3	499	500
81	4-MeO-phenylethyl	4-F-benzyl	Allyl	OCH_3	511	512
82	4-MeO-phenylethyl	2-Cl-benzyl	Allyl	OCH_3	527	528
83	4-MeO-phenylethyl	2,4-Cl_2-benzyl	Allyl	OCH_3	561	562

84	4-MeO-phenylethyl	Naphth-2-ylmethyl	Allyl	OCH_3	543	544
85	4-MeO-phenylethyl	4-HO-benzyl	Benzyl	OCH_3	559	560
86	4-MeO-phenylethyl	4-NO_2-benzyl	Benzyl	OCH_3	588	589
87	4-MeO-phenylethyl	2,4-F_2-benzyl	Benzyl	OCH_3	579	580
88	4-MeO-phenylethyl	4-Cl-benzyl	Benzyl	OCH_3	577	578
89	4-MeO-phenylethyl	2,2-bisphenylethyl	Benzyl	OCH_3	619	620
90	4-MeO-phenylethyl	3-t-Bu-4-HO-benzyl	Benzyl	OCH_3	615	616
91	4-MeO-phenylethyl	4-Me-benzyl	Benzyl	OCH_3	557	558
92	4-MeO-phenylethyl	Cyclohexylmethyl	Benzyl	OCH_3	549	550
93	4-MeO-phenylethyl	4-F-benzyl	Benzyl	OCH_3	561	562
94	4-MeO-phenylethyl	2-Cl-benzyl	Benzyl	OCH_3	577	578
95	4-MeO-phenylethyl	2,4-Cl_2-benzyl	Benzyl	OCH_3	612	613
96	4-MeO-phenylethyl	Naphth-2-ylmethyl	Benzyl	OCH_3	593	594
97	Isoamyl	4-HO-benzyl	Styrylmethyl	OCH_3	521	522
98	Isoamyl	4-NO_2-benzyl	Styrylmethyl	OCH_3	550	551
99	Isoamyl	2,4-F_2-benzyl	Styrylmethyl	OCH_3	541	542
100	Isoamyl	4-Cl-benzyl	Styrylmethyl	OCH_3	539	540
101	Isoamyl	2,2-bisphenylethyl	Styrylmethyl	OCH_3	581	582
102	Isoamyl	3-t-Bu-4-HO-benzyl	Styrylmethyl	OCH_3	497	498
103	Isoamyl	4-Me-benzyl	Styrylmethyl	OCH_3	519	520
104	Isoamyl	Cyclohexylmethyl	Styrylmethyl	OCH_3	511	512
105	Isoamyl	4-F-benzyl	Styrylmethyl	OCH_3	523	524
106	Isoamyl	2-Cl-benzyl	Styrylmethyl	OCH_3	539	540
107	Isoamyl	2,4-Cl_2-benzyl	Styrylmethyl	OCH_3	574	575
108	Isoamyl	Naphth-2-ylmethyl	Styrylmethyl	OCH_3	555	556
109	Isoamyl	4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	563	564
110	Isoamyl	4-NO_2-benzyl	2,6-Cl_2-benzyl	OCH_3	592	593
111	Isoamyl	2,4-F_2-benzyl	2,6-Cl_2-benzyl	OCH_3	583	584
112	Isoamyl	4-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	582	583
113	Isoamyl	2,2-bisphenylethyl	2,6-Cl_2-benzyl	OCH_3	624	625
114	Isoamyl	3-t-Bu-4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	540	541
115	Isoamyl	4-Me-benzyl	2,6-Cl_2-benzyl	OCH_3	562	563
116	Isoamyl	Cyclohexylmethyl	2,6-Cl_2-benzyl	OCH_3	554	555
117	Isoamyl	4-F-benzyl	2,6-Cl_2-benzyl	OCH_3	565	566
118	Isoamyl	2-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	582	583
119	Isoamyl	2,4-Cl_2-benzyl	2,6-Cl_2-benzyl	OCH_3	616	617
120	Isoamyl	Naphth-2-ylmethyl	2,6-Cl_2-benzyl	OCH_3	598	599
121	3-MeO-propyl	4-HO-benzyl	Styrylmethyl	OCH_3	523	524
122	3-MeO-propyl	4-NO_2-benzyl	Styrylmethyl	OCH_3	552	553
123	3-MeO-propyl	2,4-F_2-benzyl	Styrylmethyl	OCH_3	543	544
124	3-MeO-propyl	4-Cl-benzyl	Styrylmethyl	OCH_3	541	542
125	3-MeO-propyl	2,2-bisphenylethyl	Styrylmethyl	OCH_3	583	584
126	3-MeO-propyl	3-t-Bu-4-HO-benzyl	Styrylmethyl	OCH_3	499	500
127	3-MeO-propyl	4-Me-benzyl	Styrylmethyl	OCH_3	521	522
128	3-MeO-propyl	Cyclohexyl-methyl	Styrylmethyl	OCH_3	513	514
129	3-MeO-propyl	4-F-benzyl	Styrylmethyl	OCH_3	525	526
130	3-MeO-propyl	2-Cl-benzyl	Styrylmethyl	OCH_3	541	542
131	3-MeO-propyl	2,4-Cl_2-benzyl	Styrylmethyl	OCH_3	575	576
132	3-MeO-propyl	Naphth-2-ylmethyl	Styrylmethyl	OCH_3	557	558
133	3-MeO-propyl	4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	565	566
134	3-MeO-propyl	4-NO_2-benzyl	2,6-Cl_2-benzyl	OCH_3	594	595
135	3-MeO-propyl	2,4-F_2-benzyl	2,6-Cl_2-benzyl	OCH_3	585	586
136	3-MeO-propyl	4-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	584	585
137	3-MeO-propyl	2,2-bisphenylethyl	2,6-Cl_2-benzyl	OCH_3	626	627
138	3-MeO-propyl	3-t-Bu-4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	541	542
139	3-MeO-propyl	4-Me-benzyl	2,6-Cl_2-benzyl	OCH_3	563	564
140	3-MeO-propyl	Cyclohexyl-methyl	2,6-Cl_2-benzyl	OCH_3	556	557
141	3-MeO-propyl	4-F-benzyl	2,6-Cl_2-benzyl	OCH_3	567	568
142	3-MeO-propyl	2-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	584	585
143	3-MeO-propyl	2,4-Cl_2-benzyl	2,6-Cl_2-benzyl	OCH_3	618	619

144	3-MeO-propyl	Naphth-2-ylmethyl	2,6-Cl_2-benzyl	OCH_3	600	601
145	4-MeO-phenylethyl	4-HO-benzyl	Styrylmethyl	OCH_3	585	586
146	4-MeO-phenylethyl	4-NO_2-benzyl	Styrylmethyl	OCH_3	614	615
147	4-MeO-phenylethyl	2,4-F_2-benzyl	Styrylmethyl	OCH_3	605	606
148	4-MeO-phenylethyl	4-Cl-benzyl	Styrylmethyl	OCH_3	603	604
149	4-MeO-phenylethyl	2,2-bisphenylethyl	Styrylmethyl	OCH_3	645	646
150	4-MeO-phenylethyl	3-t-Bu-4-HO-benzyl	Styrylmethyl	OCH_3	561	562
151	4-MeO-phenylethyl	4-Me-benzyl	Styrylmethyl	OCH_3	583	584
152	4-MeO-phenylethyl	Cyclohexyl-methyl	Styrylmethyl	OCH_3	575	576
153	4-MeO-phenylethyl	4-F-benzyl	Styrylmethyl	OCH_3	587	588
154	4-MeO-phenylethyl	2-Cl-benzyl	Styrylmethyl	OCH_3	603	604
155	4-MeO-phenylethyl	2,4-Cl_2-benzyl	Styrylmethyl	OCH_3	638	639
156	4-MeO-phenylethyl	Naphth-2-ylmethyl	Styrylmethyl	OCH_3	619	620
157	4-MeO-phenylethyl	4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	628	629
158	4-MeO-phenylethyl	4-NO_2-benzyl	2,6-Cl_2-benzyl	OCH_3	657	658
159	4-MeO-phenylethyl	2,4-F_2-benzyl	2,6-Cl_2-benzyl	OCH_3	648	649
160	4-MeO-phenylethyl	4-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	646	647
161	4-MeO-phenylethyl	2,2-bisphenylethyl	2,6-Cl_2-benzyl	OCH_3	688	689
162	4-MeO-phenylethyl	3-t-Bu-4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	604	605
163	4-MeO-phenylethyl	4-Me-benzyl	2,6-Cl_2-benzyl	OCH_3	626	627
164	4-MeO-phenylethyl	Cyclohexylmethyl	2,6-Cl_2-benzyl	OCH_3	618	619
165	4-MeO-phenylethyl	4-F-benzyl	2,6-Cl_2-benzyl	OCH_3	630	631
166	4-MeO-phenylethyl	2-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	646	647
167	4-MeO-phenylethyl	2,4-Cl_2-benzyl	2,6-Cl_2-benzyl	OCH_3	680	681
168	4-MeO-phenylethyl	Naphth-2-ylmethyl	2,6-Cl_2-benzyl	OCH_3	662	663
169	Tetrahydrofuran-2-ylmethyl	4-HO-benzyl	Styrylmethyl	OCH_3	535	536
170	Tetrahydrofuran-2-ylmethyl	4-NO_2-benzyl	Styrylmethyl	OCH_3	564	565
171	Tetrahydrofuran-2-ylmethyl	2,4-F_2-benzyl	Styrylmethyl	OCH_3	555	556
172	Tetrahydrofuran-2-ylmethyl	4-Cl-benzyl	Styrylmethyl	OCH_3	553	554
173	Tetrahydrofuran-2-ylmethyl	2,2-bisphenylethyl	Styrylmethyl	OCH_3	595	596
174	Tetrahydrofuran-2-ylmethyl	3-t-Bu-4-HO-benzyl	Styrylmethyl	OCH_3	511	512
175	Tetrahydrofuran-2-ylmethyl	4-Me-benzyl	Styrylmethyl	OCH_3	533	534
176	Tetrahydrofuran-2-ylmethyl	Cyclohexyl-methyl	Styrylmethyl	OCH_3	525	526
177	Tetrahydrofuran-2-ylmethyl	4-F-benzyl	Styrylmethyl	OCH_3	537	538
178	Tetrahydrofuran-2-ylmethyl	2-Cl-benzyl	Styrylmethyl	OCH_3	553	554
179	Tetrahydrofuran-2-ylmethyl	2,4-Cl_2-benzyl	Styrylmethyl	OCH_3	588	589
180	Tetrahydrofuran-2-ylmethyl	Naphth-2-ylmethyl	Styrylmethyl	OCH_3	569	570
181	Tetrahydrofuran-2-ylmethyl	4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	577	578
182	Tetrahydrofuran-2-ylmethyl	4-NO_2-benzyl	2,6-Cl_2-benzyl	OCH_3	606	607
183	Tetrahydrofuran-2-ylmethyl	2,4-F_2-benzyl	2,6-Cl_2-benzyl	OCH_3	597	598
184	Tetrahydrofuran-2-ylmethyl	4-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	596	597
185	Tetrahydrofuran-2-ylmethyl	2,2-bisphenylethyl	2,6-Cl_2-benzyl	OCH_3	638	639
186	Tetrahydrofuran-2-ylmethyl	3-t-Bu-4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	553	554

187	Tetrahydrofuran-2-ylmethyl	4-Me-benzyl	2,6-Cl_2-benzyl	OCH_3	575	576
188	Tetrahydrofuran-2-ylmethyl	Cyclohexyl-methyl	2,6-Cl_2-benzyl	OCH_3	568	569
189	Tetrahydrofuran-2-ylmethyl	4-F-benzyl	2,6-Cl_2-benzyl	OCH_3	579	580
190	Tetrahydrofuran-2-ylmethyl	2-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	596	597
191	Tetrahydrofuran-2-ylmethyl	2,4-Cl_2-benzyl	2,6-Cl_2-benzyl	OCH_3	630	631
192	Tetrahydrofuran-2-ylmethyl	Naphth-2-ylmethyl	2,6-Cl_2-benzyl	OCH_3	612	613
193	Phenethyl	4-HO-benzyl	Methyl	(4-Me-phenyl)amino	528	529
194	Phenethyl	4-HO-benzyl	Methyl	(4-Cl-phenyl)amino	548	549
195	Phenethyl	4-HO-benzyl	Methyl	Phenylamino	514	515
196	Phenethyl	4-HO-benzyl	Methyl	((*R*)-α -methylbenzyl)amino	542	543
197	Phenethyl	4-HO-benzyl	Methyl	Benzylamino	528	529
198	Phenethyl	4-HO-benzyl	Methyl	(4-MeO-phenyl)amino	544	545
199	Phenethyl	4-HO-benzyl	Methyl	(4-Br-phenyl)amino	592	593
200	Phenethyl	4-HO-benzyl	Methyl	(4-CF_3-phenyl)amino	582	583
201	Phenethyl	4-HO-benzyl	Methyl	Pentylamino	508	509
202	Phenethyl	4-HO-benzyl	Methyl	(2-Phenylethyl) amino	542	543
203	Phenethyl	4-HO-benzyl	Methyl	(4-MeO-benzyl)amino	558	559
204	Phenethyl	4-HO-benzyl	Methyl	Cyclohexylamino	520	521
205	2,2-bisphenylethyl	4-HO-benzyl	Methyl	(4-Me-phenyl)amino	604	605
206	2,2-bisphenylethyl	4-HO-benzyl	Methyl	(4-Cl-phenyl)amino	624	625
207	2,2-bisphenylethyl	4-HO-benzyl	Methyl	Phenylamino	590	591
208	2,2-bisphenylethyl	4-HO-benzyl	Methyl	((*R*)-α -methylbenzyl)amino	618	619
209	2,2-bisphenylethyl	4-HO-benzyl	Methyl	Benzylamino	604	605
210	2,2-bisphenylethyl	4-HO-benzyl	Methyl	(4-MeO-phenyl)amino	620	621
211	2,2-bisphenylethyl	4-HO-benzyl	Methyl	(4-Br-phenyl)amino	669	670
212	2,2-bisphenylethyl	4-HO-benzyl	Methyl	(4-CF_3-phenyl)amino	658	659
213	2,2-bisphenylethyl	4-HO-benzyl	Methyl	Pentylamino	584	585
214	2,2-bisphenylethyl	4-HO-benzyl	Methyl	(2-Phenylethyl) amino	618	619
215	2,2-bisphenylethyl	4-HO-benzyl	Methyl	(4-MeO-benzyl)amino	634	635
216	2,2-bisphenylethyl	4-HO-benzyl	Methyl	Cyclohexylamino	596	597
217	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-Me-phenyl)amino	581	582
218	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-Cl-phenyl)amino	601	602
219	Phenethyl	3,4-Cl_2-benzyl	Methyl	Phenylamino	566	567
220	Phenethyl	3,4-Cl_2-benzyl	Methyl	((*R*)-α -methylbenzyl)amino	595	596
221	Phenethyl	3,4-Cl_2-benzyl	Methyl	Benzylamino	581	582
222	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-phenyl)amino	597	598
223	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-Br-phenyl)amino	645	646
224	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-CF_3-phenyl)amino	634	635
225	Phenethyl	3,4-Cl_2-benzyl	Methyl	Pentylamino	561	562
226	Phenethyl	3,4-Cl_2-benzyl	Methyl	(2-Phenylethyl) amino	595	596
227	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-benzyl)amino	611	612
228	Phenethyl	3,4-Cl_2-benzyl	Methyl	Cyclohexylamino	573	574
229	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-Me-phenyl)amino	657	658
230	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-Cl-phenyl)amino	677	678
231	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	Phenylamino	643	644
232	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	((*R*)-α-methylbenzyl)amino	671	672
233	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	Benzylamino	657	658
234	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-phenyl)amino	673	674
235	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-Br-phenyl)amino	721	722
236	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-CF_3-phenyl)amino	711	712
237	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	Pentylamino	637	638
238	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(2-Phenylethyl) amino	671	672
239	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-benzyl)amino	687	688
240	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	Cyclohexylamino	649	650

241	Isoamyl	4-HO-benzyl	Methyl	(4-Me-phenyl)amino	478	479
242	Isoamyl	4-HO-benzyl	Methyl	(4-Cl-phenyl)amino	498	499
243	Isoamyl	4-HO-benzyl	Methyl	Phenylamino	464	465
244	Isoamyl	4-HO-benzyl	Methyl	((*R*)-α-methylbenzyl)amino	492	493
245	Isoamyl	4-HO-benzyl	Methyl	Benzylamino	478	479
246	Isoamyl	4-HO-benzyl	Methyl	(4-MeO-phenyl)amino	494	495
247	Isoamyl	4-HO-benzyl	Methyl	(4-Br-phenyl)amino	542	543
248	Isoamyl	4-HO-benzyl	Methyl	(4-CF_3-phenyl)amino	532	533
249	Isoamyl	4-HO-benzyl	Methyl	Pentylamino	458	459
250	Isoamyl	4-HO-benzyl	Methyl	(2-Phenylethyl) amino	492	493
251	Isoamyl	4-HO-benzyl	Methyl	(4-MeO-benzyl)amino	508	509
252	Isoamyl	4-HO-benzyl	Methyl	Cyclohexylamino	470	471
253	Isoamyl	4-HO-benzyl	Methyl	(4-Me-phenyl)amino	554	555
254	Isoamyl	4-HO-benzyl	Methyl	(4-Cl-phenyl)amino	574	575
255	Isoamyl	4-HO-benzyl	Methyl	Phenylamino	540	541
256	Isoamyl	4-HO-benzyl	Methyl	((*R*)-α-methylbenzyl)amino	568	569
257	Isoamyl	4-HO-benzyl	Methyl	Benzylamino	554	555
258	Isoamyl	4-HO-benzyl	Methyl	(4-MeO-phenyl)amino	570	571
259	Isoamyl	4-HO-benzyl	Methyl	(4-Br-phenyl)amino	619	620
260	Isoamyl	4-HO-benzyl	Methyl	(4-CF_3-phenyl)amino	608	609
261	Isoamyl	4-HO-benzyl	Methyl	Pentylamino	534	535
262	Isoamyl	4-HO-benzyl	Methyl	(2-Phenylethyl) amino	568	569
263	Isoamyl	4-HO-benzyl	Methyl	(4-MeO-benzyl)amino	584	585
264	Isoamyl	4-HO-benzyl	Methyl	Cyclohexylamino	546	547
265	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Me-phenyl)amino	526	527
266	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Cl-phenyl)amino	546	547
267	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Phenylamino	512	513
268	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	((*R*)-α-methylbenzyl)amino	540	541
269	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Benzylamino	526	527
270	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-phenyl)amino	542	543
271	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Br-phenyl)amino	591	592
272	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-CF_3-phenyl)amino	580	581
273	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Pentylamino	506	507
274	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(2-Phenylethyl) amino	540	541
275	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-benzyl)amino	556	557
276	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Cyclohexylamino	518	519
277	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Me-phenyl)amino	602	603
278	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Cl-phenyl)amino	622	623
279	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Phenylamino	588	589
280	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	((*R*)-α-methylbenzyl)amino	616	617
281	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Benzylamino	602	603
282	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-phenyl)amino	618	619
283	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Br-phenyl)amino	667	668
284	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-CF_3-phenyl)amino	656	657
285	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Pentylamino	582	583
286	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(2-Phenylethyl)amino	616	617
287	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-benzyl)amino	632	633
288	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Cyclohexylamino	594	595
289	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	(N-Cbz-3-Indoleethyl)amino	751	752
290	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	(Naphth-2-ylmethyl)amino	614	615
291	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	(2-Phenylethyl)amino	578	579
292	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	[2-(4-MeO-phenyl)ethyl]amino	608	609
293	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	(3-CF_3-benzyl)amino	632	633
294	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	(4-MeO-benzyl)amino	594	595
295	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	(4-F-phenylethyl)amino	596	597
296	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	(3,4-Cl_2-benzyl)amino	633	634
297	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	(2-HO-ethyl)amino	518	519
298	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	(3-MeO-propyl)amino	546	547
299	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	(Tetrahydrofuran-2-ylmethyl)amino	558	559

300	Naphth-1-ylmethyl	4-HO-benzyl	Methyl	(cyclohexylmethyl)amino	570	571
301	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	(N-Cbz-3-Indoleethyl)amino	779	780
302	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	(Naphth-2-ylmethyl)amino	642	643
303	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	(2-Phenylethyl)amino	606	607
304	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	[2-(4-MeO-phenyl)ethyl]amino	636	637
305	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	(3-CF_3-benzyl)amino	660	661
306	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	(4-MeO-benzyl)amino	622	623
307	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	(4-F-phenylethyl)amino	624	625
308	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	(3,4-Cl_2-benzyl)amino	661	662
309	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	(2-HO-ethyl)amino	546	547
310	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	(3-MeO-propyl)amino	574	575
311	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	(Tetrahydrofuran-2-ylmethyl)amino	586	587
312	Naphth-1-ylmethyl	4-HO-benzyl	Propyl	(cyclohexylmethyl)amino	598	599
313	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(N-Cbz-3-Indoleethyl)amino	771	772
314	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(Naphth-2-ylmethyl)amino	634	635
315	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(2-Phenylethyl)amino	598	599
316	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	[2-(4-MeO-phenyl)ethyl]amino	628	629
317	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(3-CF_3-benzyl)amino	652	653
318	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(4-MeO-benzyl)amino	614	615
319	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(4-F-phenylethyl)amino	616	617
320	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(3,4-Cl_2-benzyl)amino	653	654
321	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(2-HO-ethyl)amino	538	539
322	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(3-MeO-propyl)mino	566	567
323	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(Tetrahydrofuran-2-ylmethyl)amino	578	579
324	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(cyclohexylmethyl)amino	590	591
325	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(N-Cbz-3-Indoleethyl)amino	799	800
326	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(Naphth-2-ylmethyl)amino	662	663
327	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(2-Phenylethyl)amino	626	627
328	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	[2-(4-MeO-phenyl)ethyl]amino	656	657
329	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(3-CF_3-benzyl)amino	680	681
330	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(4-MeO-benzyl)amino	642	643
331	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(4-F-phenylethyl)amino	644	645
332	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(3,4-Cl_2-benzyl)amino	681	682
333	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(2-HO-ethyl)amino	566	567
334	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(3-MeO-propyl)mino	594	595
335	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(Tetrahydrofuran-2-ylmethyl)amino	606	607
336	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(cyclohexylmethyl)amino	618	619
337	Naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(N-Cbz-3-Indoleethyl)amino	811	812
338	Naphth-1-ylmethyl	4-biphenylylmethyl	Methyl	(Naphth-2-ylmethyl)amino	674	675
339	Naphth-1-ylmethyl	4-biphenylylmethyl	Methyl	(2-Phenylethyl)amino	638	639
340	Naphth-1-ylmethyl	4-biphenylylmethyl	Methyl	[2-(4-MeO-phenyl)ethyl]amino	668	669
341	Naphth-1-ylmethyl	4-biphenylylmethyl	Methyl	(3-CF_3-benzyl)amino	692	693
342	Naphth-1-ylmethyl	4-biphenylylmethyl	Methyl	(4-MeO-benzyl)amino	654	655
343	Naphth-1-ylmethyl	4-biphenylylmethyl	Methyl	(4-F-phenylethyl)amino	656	657
344	Naphth-1-ylmethyl	4-biphenylylmethyl	Methyl	(3,4-Cl_2-benzyl)amino	693	694
345	Naphth-1-ylmethyl	4-biphenylylmethyl	Methyl	(2-HO-ethyl)amino	578	579
346	Naphth-1-ylmethyl	4-biphenylylmethyl	Methyl	(3-MeO-propyl)mino	606	607
347	Naphth-1-ylmethyl	4-biphenylylmethyl	Methyl	(Tetrahydrofuran-2-ylmethyl)amino	618	619
348	Naphth-1-ylmethyl	4-biphenylylmethyl	Methyl	(cyclohexylmethyl)amino	630	631
349	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	(N-Cbz-3-Indoleethyl)amino	839	840
350	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	(Naphth-2-ylmethyl)amino	702	703
351	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	(2-Phenylethyl)amino	666	667
352	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	[2-(4-MeO-phenyl)ethyl]amino	696	697
353	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	(3-CF_3-benzyl)amino	720	721
354	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	(4-MeO-benzyl)amino	682	683
355	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	(4-F-phenylethyl)amino	684	685

356	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	(3,4-Cl_2-benzyl)amino	721	722
357	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	(2-HO-ethyl)amino	606	607
358	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	(3-MeO-propyl)mino	634	635
359	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	(Tetrahydrofuran-2-ylmethyl)amino	646	647
360	Naphth-1-ylmethyl	4-biphenylylmethyl	Propyl	(cyclohexylmethyl)amino	658	659
361	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	(N-Cbz-3-Indoleethyl)amino	807	808
362	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	(Naphth-2-ylmethyl)amino	670	671
363	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	(2-Phenylethyl)amino	634	635
364	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	[2-(4-MeO-phenyl)ethyl]amino	664	665
365	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	(3-CF_3-benzyl)amino	688	689
366	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	(4-MeO-benzyl)amino	650	651
367	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	(4-F-phenylethyl)amino	652	653
368	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	(3,4-Cl_2-benzyl)amino	689	690
369	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	(2-HO-ethyl)amino	574	575
370	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	(3-MeO-propyl)mino	602	603
371	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	(Tetrahydrofuran-2-ylmethyl)amino	614	615
372	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	(cyclohexylmethyl)amino	626	627
373	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	(N-Cbz-3-Indoleethyl)amino	835	836
374	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	(Naphth-2-ylmethyl)amino	698	699
375	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	(2-Phenylethyl)amino	662	663
376	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	[2-(4-MeO-phenyl)ethyl]amino	692	693
377	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	(3-CF_3-benzyl)amino	716	717
378	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	(4-MeO-benzyl)amino	678	679
379	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	(4-F-phenylethyl)amino	680	681
380	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	(3,4-Cl_2-benzyl)amino	717	718
381	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	(2-HO-ethyl)amino	602	603
382	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	(3-MeO-propyl)mino	630	631
383	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	(Tetrahydrofuran-2-ylmethyl)amino	642	643
384	Naphth-1-ylmethyl	3-t-Bu-4-HO-benzyl	Propyl	(cyclohexylmethyl)amino	654	655
385	4-Methoxybenzyl	OCH_3	5-F-benzyl	OCH_3	470	471
386	Naphthyl-1-ylmethyl	4-HO-benzyl	Styrylmethyl	OCH_3	591	592
387	Naphthyl-1-ylmethyl	4-NO_2-benzyl	Styrylmethyl	OCH_3	620	621
388	Naphthyl-1-ylmethyl	3,4-F_2-benzyl	Styrylmethyl	OCH_3	611	612
389	Naphthyl-1-ylmethyl	4-Cl-benzyl	Styrylmethyl	OCH_3	609	610
390	Naphthyl-1-ylmethyl	4-Phenyl-benzyl	Styrylmethyl	OCH_3	651	652
391	Naphthyl-1-ylmethyl	3-t-Bu-4-HO-benzyl	Styrylmethyl	OCH_3	647	648
392	Naphthyl-1-ylmethyl	4-Methyl-benzyl	Styrylmethyl	OCH_3	589	590
393	Naphthyl-1-ylmethyl	Cyclohexylmethyl	Styrylmethyl	OCH_3	581	582
394	Naphthyl-1-ylmethyl	4-F-benzyl	Styrylmethyl	OCH_3	593	594
395	Naphthyl-1-ylmethyl	2-Cl-benzyl	Styrylmethyl	OCH_3	609	610
396	Naphthyl-1-ylmethyl	3,4-Cl_2-benzyl	Styrylmethyl	OCH_3	644	645
397	Naphthyl-1-ylmethyl	Naphthyl-1-ylmethyl	Styrylmethyl	OCH_3	625	626
398	3,4-Cl_2-benzyl	4-HO-benzyl	Styrylmethyl	OCH_3	610	611
399	3,4-Cl_2-benzyl	4-NO_2-benzyl	Styrylmethyl	OCH_3	639	640
400	3,4-Cl_2-benzyl	3,4-F_2-benzyl	Styrylmethyl	OCH_3	629	630
401	3,4-Cl_2-benzyl	4-Cl-benzyl	Styrylmethyl	OCH_3	628	629
402	3,4-Cl_2-benzyl	4-Phenyl-benzyl	Styrylmethyl	OCH_3	670	671
403	3,4-Cl_2-benzyl	3-t-Bu-4-HO-benzyl	Styrylmethyl	OCH_3	666	667
404	3,4-Cl_2-benzyl	4-Methyl-benzyl	Styrylmethyl	OCH_3	608	609
405	3,4-Cl_2-benzyl	Cyclohexylmethyl	Styrylmethyl	OCH_3	600	601
406	3,4-Cl_2-benzyl	4-F-benzyl	Styrylmethyl	OCH_3	611	612
407	3,4-Cl_2-benzyl	2-Cl-benzyl	Styrylmethyl	OCH_3	628	629
408	3,4-Cl_2-benzyl	3,4-Cl_2-benzyl	Styrylmethyl	OCH_3	662	663
409	3,4-Cl_2-benzyl	Naphthyl-1-ylmethyl	Styrylmethyl	OCH_3	644	645
410	Naphthyl-1-ylmethyl	4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	634	635
411	Naphthyl-1-ylmethyl	4-NO_2-benzyl	2,6-Cl_2-benzyl	OCH_3	663	664
412	Naphthyl-1-ylmethyl	3,4-F_2-benzyl	2,6-Cl_2-benzyl	OCH_3	654	655
413	Naphthyl-1-ylmethyl	4-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	652	653

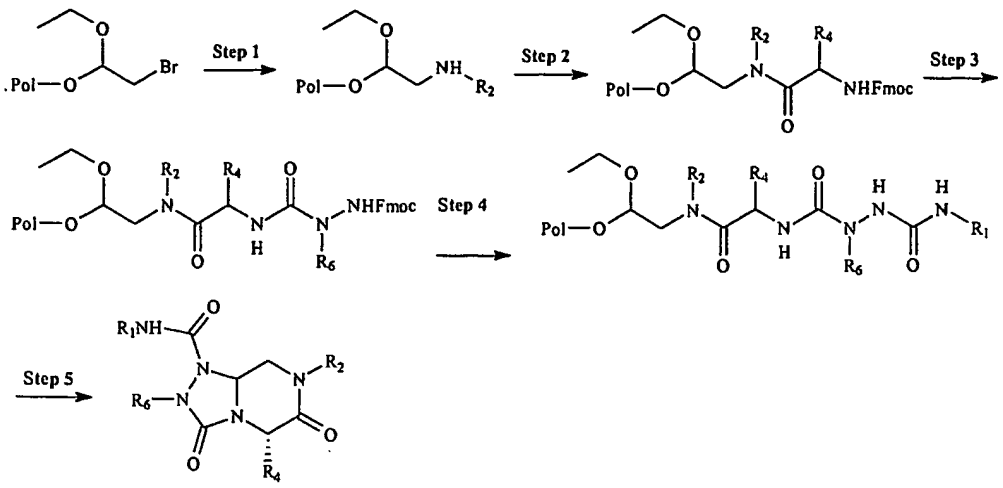
414	Naphthyl-1-ylmethyl	4-Phenyl-benzyl	2,6-Cl_2-benzyl	OCH_3	694	695
415	Naphthyl-1-ylmethyl	3-t-Bu-4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	690	691
416	Naphthyl-1-ylmethyl	4-Methyl-benzyl	2,6-Cl_2-benzyl	OCH_3	632	633
417	Naphthyl-1-ylmethyl	Cyclohexylmethyl	2,6-Cl_2-benzyl	OCH_3	624	625
418	Naphthyl-1-ylmethyl	4-F-benzyl	2,6-Cl_2-benzyl	OCH_3	636	637
419	Naphthyl-1-ylmethyl	2-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	652	653
420	Naphthyl-1-ylmethyl	3,4-Cl_2-benzyl	2,6-Cl_2-benzyl	OCH_3	686	687
421	Naphthyl-1-ylmethyl	Naphthyl-1-ylmethyl	2,6-Cl_2-benzyl	OCH_3	668	669
422	3,4-Cl_2-benzyl	4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	652	653
423	3,4-Cl_2-benzyl	4-NO_2-benzyl	2,6-Cl_2-benzyl	OCH_3	681	682
424	3,4-Cl_2-benzyl	3,4-F_2-benzyl	2,6-Cl_2-benzyl	OCH_3	672	673
425	3,4-Cl_2-benzyl	4-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	671	672
426	3,4-Cl_2-benzyl	4-Phenyl-benzyl	2,6-Cl_2-benzyl	OCH_3	712	713
427	3,4-Cl_2-benzyl	3-t-Bu-4-HO-benzyl	2,6-Cl_2-benzyl	OCH_3	708	709
428	3,4-Cl_2-benzyl	4-Methyl-benzyl	2,6-Cl_2-benzyl	OCH_3	650	651
429	3,4-Cl_2-benzyl	Cyclohexylmethyl	2,6-Cl_2-benzyl	OCH_3	642	643
430	3,4-Cl_2-benzyl	4-F-benzyl	2,6-Cl_2-benzyl	OCH_3	654	655
431	3,4-Cl_2-benzyl	2-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	671	672
432	3,4-Cl_2-benzyl	3,4-Cl_2-benzyl	2,6-Cl_2-benzyl	OCH_3	705	706
433	3,4-Cl_2-benzyl	Naphthyl-1-ylmethyl	2,6-Cl_2-benzyl	OCH_3	686	687
434	2-Piperidin-1-yl-ethyl	(S)-4-HO-benzyl	Methyl	Benzylamino	535	536
435	3,4-Cl_2-benzyl	(S)-4-HO-benzyl	Methyl	2-Piperidin-1-yl-ethylamino	604	605
436	3,4-Cl_2-benzyl	(S)-4-HO-benzyl	Methyl	2-(1-Methyl-pyrrolidin-2-yl)-ethylamino	604	605
437	3-Pyridylmethyl	(S)-4-HO-benzyl	Methyl	3,4-Cl_2-benzylamino	583	584
438	2-Morpholin-4-yl-ethyl	(S)-4-HO-benzyl	Methyl	3,4-Cl_2-benzylamino	606	607
439	3,4-Cl_2-benzyl	(S)-4-HO-benzyl	Methyl	3-Pyridylmethylamino	583	584
440	3,4-Cl_2-benzyl	(S)-4-HO-benzyl	Methyl	2-Morpholin-4-yl-ethylamino	606	607
441	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	3-Imidazol-1-yl-propylamino	582	583
442	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	4-Aminophenethylamino	593	594
443	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	3-Pyridylmethylamino	565	566
444	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	2-(3-Pyridylethyl)amino	579	580
445	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	4-Pyridylmethylamino	565	566
446	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Benzyloxycarbonylamino	622	623
447	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	4-F-benzylamino	582	583
448	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	4-CO_2H-benzylamino	608	609
449	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	4-CF_3-benzylamino	632	633
450	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	(S)-alpha-methylbenzylamino	578	579
451	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	(R)-alpha-methylbenzylamino	578	579
452	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	2-F-benzylamino	582	583
453	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	2,3-Dimethoxybenzylamino	624	625
454	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Cyanomethylamino	513	514
455	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Phenylhydrazino	565	566
456	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	4-Aminobenzylamino	579	580
457	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	(S,S) {2-[(2-hydroxy-1-methyl-2-phenyl-ethyl)-methyl-carbamoyl]-ethyl}-amino	693	694
458	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	[4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-cyclohexyl]-methylamino	715	716
459	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Indan-1-ylamino	590	591
460	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	PhenylGlycine	622	623
461	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	2,6-F_2-benzylamino	600	601
462	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	3-F-benzylamino	582	583
463	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Benzimidazol-2-yl-amino	604	605
464	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Diphenylmethylamino	640	641
465	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Furan-2-yl-methylamino	554	555
466	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	4-Dimethylamino-benzylamino	607	608
467	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Thiofuran-2-yl-methylamino	584	585
468	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	4-NO_2-benzylamino	609	610
469	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	BnO	565	566
470	4-Methoxy-naphthyl-1-	4-HO-benzyl	Methyl	Benzylamino	594	595

	ylmethyl					
471	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Phenethyl	563	564
472	Naphthyl-1-ylmethyl	4-Methoxy-benzyl	Methyl	Benzylamino	578	579
473	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	4-CF_3-phenylamino	618	619
474	Naphthyl-1-ylmethyl	4-NO_2-benzyl	Methyl	4-CF_3-phenylamino	647	648
475	Naphthyl-1-ylmethyl	4-NO_2-benzyl	Methyl	Benzylamino	593	594
476	Benzyl	Naphthyl-1-ylmethyl	4-CN-benzyl	OCH_3	574	575
477	Thiofuran-2-yl-methyl	Naphthyl-1-ylmethyl	4-CN-benzyl	OCH_3	594	595
478	4-Dimethylamino-benzyl	Naphthyl-1-ylmethyl	4-CN-benzyl	OCH_3	617	618
479	Phenethyl	Naphthyl-1-ylmethyl	4-CN-benzyl	OCH_3	588	589
480	8-Quinoline-1yl-methyl	4-HO-benzyl	Methyl	Benzylamino	565	566
481	4-Pyridylmethyl	Naphthyl-1-ylmethyl	Benzyl	OCH_3	550	551
482	3,4-Dimethoxybenzyl	Naphthyl-1-ylmethyl	Benzyl	OCH_3	609	610
483	3,4-Dimethoxy-phenethyl	Naphthyl-1-ylmethyl	Benzyl	OCH_3	623	624
484	Thiofuran-2-yl-methyl	Naphthyl-1-ylmethyl	Benzyl	OCH_3	569	570
485	Naphthyl-1-ylmethyl	3-Pyridylmethyl	Methyl	Benzylamino	549	550
486	Naphthyl-1-ylmethyl	Pentafluorobenzyl	Methyl	Benzylamino	638	639
487	Naphthyl-1-ylmethyl	3-F-4-HO-benzyl	Methyl	Benzylamino	582	583
488	4-F-phenethyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	598	599
489	4-Methoxyphenethyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	610	611
490	3,4-Dimethoxy-phenethyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	640	641
491	Naphthyl-1-ylmethyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	616	617
492	3,4-Dimethoxybenzyl	Naphthyl-1-ylmethyl	4-CN-benzyl	OCH_3	634	635
493	3,4-Dimethoxy-phenethyl	Naphthyl-1-ylmethyl	4-CN-benzyl	OCH_3	648	649
494	4-Quinoline-1yl-methyl	4-HO-benzyl	Methyl	Benzylamino	565	566
495	2-Pyridylmethyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	567	568
496	3-Pyridylmethyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	567	568
497	3,4-Dimethoxybenzyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	626	627
498	4-Methyl-benzyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	580	581
499	Thiofuran-2-yl-methyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	572	573
500	4-CF_3-benzyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	634	635
501	2,6-F_2-benzyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	602	603
502	4-F-benzyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	584	585
503	Thiofuran-2-yl-ethyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	586	587
504	3,4-Cl_2-benzyl	4-Methyl-benzyl	Methyl	4-CF_3-phenylamino	634	635
505	4-CO2H-Benzyl	4-HO-benzyl	Methyl	Benzylamino	558	559
506	Naphthyl-1-ylmethyl	3-t-Bu-4-HO-benzyl	Methyl	Benzylamino	620	621
507	Naphthyl-1-ylmethyl	3,4-(OH)2-benzyl	Methyl	Benzylamino	580	581
508	2-F-benzyl	4-HO-benzyl	Methyl	Benzylamino	532	533
509	3-F-benzyl	4-HO-benzyl	Methyl	Benzylamino	532	533
510	4-F-benzyl	4-HO-benzyl	Methyl	Benzylamino	532	533
511	2,4-F_2-benzyl	4-HO-benzyl	Methyl	Benzylamino	550	551
512	2,6-F_2-benzyl	4-HO-benzyl	Methyl	Benzylamino	550	551
513	2,5-F_2-benzyl	4-HO-benzyl	Methyl	Benzylamino	550	551
514	3-CF_3-benyl	4-HO-benzyl	Methyl	Benzylamino	582	583
515	4-CF_3-benyl	4-HO-benzyl	Methyl	Benzylamino	582	583
516	3,4,5-F_3-benyl	4-HO-benzyl	Methyl	Benzylamino	568	569
517	2-Cl-benzyl	4-HO-benzyl	Methyl	Benzylamino	548	549
518	3-Cl-benzyl	4-HO-benzyl	Methyl	Benzylamino	548	549
519	2,4-Cl_2-benzyl	4-HO-benzyl	Methyl	Benzylamino	582	583
520	(S)-Methylphenyl	4-HO-benzyl	Methyl	Benzylamino	528	529
521	(R)-Methylphenyl	4-HO-benzyl	Methyl	Benzylamino	528	529
522	4-Methyl-benzyl	4-HO-benzyl	Methyl	Benzylamino	528	529
523	4-Methoxybenzyl	4-HO-benzyl	Methyl	Benzylamino	544	545
524	3,4-Dimethoxybenzyl	4-HO-benzyl	Methyl	Benzylamino	574	575
525	Furan-2-yl-methylamino	4-HO-benzyl	Methyl	Benzylamino	504	505
526	(R)-Methylnaphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Benzylamino	578	579

527	(S)-Methylnaphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Benzylamino	578	579
528	Naphthyl-1-ylmethyl	3-Oxy-pyridin-1-ylmethyl	Methyl	Benzylamino	565	566
529	(R)-alpha-methylbenzyl	4-HO-benzyl	Methyl	Benzylamino	578	579
530	Naphthyl-2-ylmethyl	4-HO-benzyl	Methyl	Benzylamino	564	565
531	4-F-naphthyl-1-ylmethy	4-HO-benzyl	Methyl	Benzylamino	582	583
532	2-Methoxybenzyl	4-HO-benzyl	Methyl	Benzylamino	544	545
533	4-Cl-benzyl	4-HO-benzyl	Methyl	Benzylamino	548	549
534	3,4-Cl_2-benzyl	4-HO-benzyl	Methyl	Benzylamino	582	583
535	2-CF_3Obenzyl	4-HO-benzyl	Methyl	Benzylamino	598	599
536	2-CF_3Sbenzyl	4-HO-benzyl	Methyl	Benzylamino	614	615
537	2-CF_3benzyl	4-HO-benzyl	Methyl	Benzylamino	582	583
538	5-Quinoline-1yl-methyl	4-HO-benzyl	Methyl	Benzylamino	565	566
539	8-Quinoline-1yl-methyl	3-t-Bu-4-HO-benzyl	Methyl	Benzylamino	621	622
540	8-Quinoline-1yl-methyl	4-NO_2-benzyl	Methyl	Benzylamino	594	595
541	8-Quinoline-1yl-methyl	(1H-Pyrrol-2-yl)-methyl	Methyl	Benzylamino	538	539
542	Naphthyl-1-ylmethyl	4-Benzyloxy-carbonylaminobenzyl	Methyl	Benzylamino	697	698
543	2,3-Cl_2-benzyl	4-HO-benzyl	Methyl	Benzylamino	582	583
544	Pentafluorobenzyl	4-HO-benzyl	Methyl	Benzylamino	604	605
545	Benzyl	4-HO-benzyl	Methyl	Benzylamino	514	515
546	Quinoxaline-5yl-methyl	4-HO-benzyl	Methyl	Benzylamino	566	567
547	8-Quinoline-1yl-methyl	3-Pyridylmethyl	Methyl	Benzylamino	550	551
548	8-Quinoline-1yl-methyl	Pentafluorobenzyl	Methyl	Benzylamino	639	640
549	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	Benzylamino(thiourea)	580	581
550	Naphthyl-1-ylmethyl	4-Amino-benzyl	Methyl	Benzylamino	563	564
551	3,4,5-tri-Methoxybenzyl	4-Amino-benzyl	Methyl	Benzylamino	603	604
552	Naphthyl-1-ylmethyl	4-Pyridylmethyl	Methyl	Benzylamino	549	550
553	Naphthyl-1-ylmethyl	(R) 4-HO-phenyl	Methyl	Benzylamino	550	551
554	2-HO-3-Methoxy-benzyl	4-HO-benzyl	Methyl	Benzylamino	560	561
555	Naphthyl-1-ylmethyl	3-Nitro-4-HO-benzyl	Methyl	Benzylamino	609	610
556	Naphthyl-1-ylmethyl	4-CO_2H-CH_2O-benzyl	Methyl	Benzylamino	622	623
557	Naphthyl-1-ylmethyl	1-Naphtoylamino-methyl	Methyl	Benzylamino	641	642
558	Naphthyl-1-ylmethyl	4-Oxy-pyridylmethyl	Methyl	Benzylamino	565	566
559	4-F-alpha-methylbenzyl	4-HO-benzyl	Methyl	Benzylamino	546	547
560	Naphthyl-1-ylmethyl	Benzoylaminoethyl	Methyl	Benzylamino	605	606
561	8-Quinoline-1yl-methyl	3,4-$(OH)_2$-benzyl	Methyl	Benzylamino	581	582
562	4-N,N-Dimethylamino-benzyl	4-HO-benzyl	Methyl	Benzylamino	557	558
563	Naphthyl-1-ylmethyl	(R) 4-F-benzyl	Methyl	Benzylamino	609	610
564	Naphthyl-1-ylmethyl	4-HO-benzyl	Methyl	2-Chloroethylamino	536	537
565	Naphthyl-1-ylmethyl	4-HO-phenethyl	Methyl	Benzylamino	578	579
566	4-F-benzyl	3-F,4-HO-benzyl	Methyl	Benzylamino	550	551
567	2,4-F_2-benzyl	3-F,4-HO-benzyl	Methyl	Benzylamino	568	569
568	3-CF_3benzyl	(R) 4-HO-phenyl	Methyl	Benzylamino	568	569
569	(S)-Methylnaphthyl-1-ylmethyl	(R) 4-HO-phenyl	Methyl	Benzylamino	514	515
570	(R)-Methylnaphthyl-1-ylmethyl	(R) 4-HO-phenyl	Methyl	Benzylamino	514	515
571	2,3,6-F_3-benzyl	(R) 4-HO-phenyl	Methyl	Benzylamino	554	555
572	3-F-benzyl	(R) 4-HO-phenyl	Methyl	Benzylamino	518	519
573	4-Cl-benzyl	(R) 4-HO-phenyl	Methyl	Benzylamino	534	535
574	3-Cl-benzyl	(R) 4-HO-phenyl	Methyl	Benzylamino	534	535
575	2-Cl-benzyl	(R) 4-HO-phenyl	Methyl	Benzylamino	534	535
576	3,4-Cl_2-benzyl	(R) 4-HO-phenyl	Methyl	Benzylamino	568	569
577	3-CF_3O-benzyl	(R) 4-HO-phenyl	Methyl	Benzylamino	584	585
578	4-F-benzyl	(R) 4-HO-phenyl	Methyl	Benzylamino	518	519

579	2,4-F_2-benzyl	(R) 4-HO-phenyl	Methyl	Benzylamino	536	537
580	3-(2-Chloro-ethyl)-ureido]-benzyl	4-HO-benzyl	Methyl	Benzylamino	634	635
581	3-Aminobenzyl	4-HO-benzyl	Methyl	Benzylamino	529	530
582	3-*N*-Methylaminobenzyl	4-HO-benzyl	Methyl	Benzylamino	543	544
583	3-*N,N*-Dimethylaminobenzyl	4-HO-benzyl	Methyl	Benzylamino	557	558
584	1H-Benzoimidazol-4-ylmethyl	4-HO-benzyl	Methyl	Benzylamino	554	555
585	2-HO-benzyl	4-HO-benzyl	Methyl	Benzylamino	530	531
586	2-Pyridylmethyl	4-HO-benzyl	Methyl	Benzylamino	515	516
587	4-Pyridylmethyl	4-HO-benzyl	Methyl	Benzylamino	515	516
588	8-quinolin-2-ylmethyl	4-HO-benzyl	Methyl	Benzylamino	565	566
589	8-Benzofuran-4-ylmethyl	4-HO-benzyl	Methyl	Benzylamino	554	555
590	Naphthyl-1-ylmethyl	4-HO-phenyl	Methyl	Benzylamino	550	551
591	4-F-benzyl	4-HO-phenyl	Methyl	Benzylamino	518	519
592	2,4-F_2-benzyl	4-HO-phenyl	Methyl	Benzylamino	536	537
593	(R)-Toluylmethyl	4-HO-benzyl	Methyl	Benzylamino	542	543
594	(S)-Toluylmethyl	4-HO-benzyl	Methyl	Benzylamino	542	543
595	1,2,3,4-tetrahydro-naphthalen-2-yl	4-HO-benzyl	Methyl	Benzylamino	554	555
596	Naphthyl-1-ylmethyl	3,4-Dimethoxybenzyl	Methyl	Benzylamino	608	609
597	2-Dimethylamino-6-F-benzyl	4-HO-benzyl	Methyl	Benzylamino	575	576
598	2-Dimethylaminobenzyl	4-HO-benzyl	Methyl	Benzylamino	557	558
599	Naphthyl-1-ylmethyl	4-CN-benzyl	Methyl	Benzylamino	573	574
600	4-F-2-CF_3-benzyl	4-HO-benzyl	Methyl	Benzylamino	599	600
601	4-Cl-2-Dimethylaminobenzyl	4-HO-benzyl	Methyl	Benzylamino	591	592
602	3-*N,N*-Ethylmethyllamino-benzyl	4-HO-benzyl	Methyl	Benzylamino	571	572
603	3-Diethylaminobenzyl	4-HO-benzyl	Methyl	Benzylamino	585	586
604	4-Cl-3-Dimethylaminobenzyl	4-HO-benzyl	Methyl	Benzylamino	591	592
605	4-F-2-Dimethylaminobenzyl	4-HO-benzyl	Methyl	Benzylamino	575	576
606	3,5-$(CH_3)_2$-2-Dimethylamino-benzyl	4-HO-benzyl	Methyl	Benzylamino	585	586
607	3-(CH_3)-2-Dimethylaminobenzyl	4-HO-benzyl	Methyl	Benzylamino	571	572
608	6-(CH_3)-2-Dimethylaminobenzyl	4-HO-benzyl	Methyl	Benzylamino	571	572
609	3,4-F_2-2-Dimethylaminobenzyl	4-HO-benzyl	Methyl	Benzylamino	593	594

In addition, synthesis of the peptide mimetics of the library of the present invention may be accomplished using the General Scheme of [4,3,0] Reverse-Turn Mimetic Library as follows:



Synthesis of the peptide mimetics of the bicyclic template libraries of the present invention was accomplished using FlexChem Reactor Block which has 96 well plate by known techniques. In the above scheme 'Pol' represents Bromoacetal resin (Advanced ChemTech) and detailed procedure is illustrated bellow.

Step 1

The bromoacetal resin (1.6mmol/g) and a solution of R1 amine in DMSO (2M solution) were placed in 96 well Robbins block (FlexChem). The reaction mixture was shaken at 60℃ using rotating oven [Robbins Scientific] for 12 hours. The resin was washed with DMF, MeOH, and then DCM

Step 2

A solution of commercial available Fmoc-Amino Acids (4 equiv.), PyBob (4 equiv.), HOAt (4 equiv.), and DIEA (12 equiv.) in DMF was added to the resin. After the reaction mixture was shaken for 12 hours at room temperature, the resin was washed with DMF, MeOH, and then DCM.

Step 3

To the resin swollen by DMF before reaction was added 25% piperidine in DMF. After the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and then washed with DMF, Methanol, then DCM. A solution of hydrazine carbamoyl chloride (4 equiv.), HOBt (4 equiv.), and DIC (4 equiv.) in DMF was added to the resin. After the reaction mixture was shaken for 12 hours at room temperature, the resin was washed with DMF, MeOH, and then DCM.

Step 4

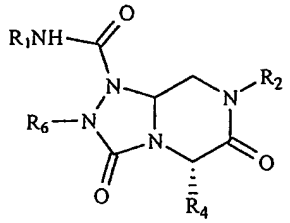
To the resin swollen by DMF before reaction was added 25% piperidine in DMF. After the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and then washed with DMF, Methanol, then DCM. To the resin swollen by DCM before reaction was added R_1-isocynate (5 equiv.) in DCM. After the reaction mixture was shaken for 12 hours at room temperature the resin was washed with DMF, MeOH, then DCM.

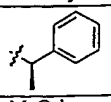
Step 5

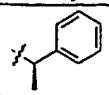
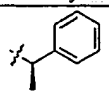
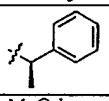
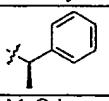
The resin was treated with formic acid (1.2 mL each well) for 18 hours at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure using SpeedVac [SAVANT] to give the product as oil. These products were diluted with 50% water/acetonitrile and then lyophilized after freezing.

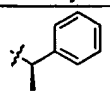
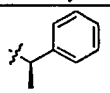
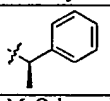
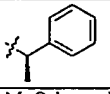
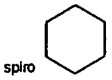
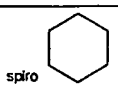
Table 3 shows a [4,3,0] Reverse turn mimetics library which can be prepared according to the present invention, of which representative preparation is given in Example 5.

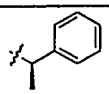
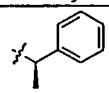
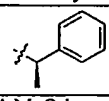
[Table 3] The [4,3,0] Reverse turn mimetics library

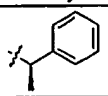
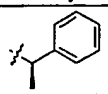
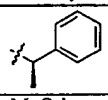
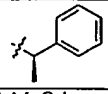


No	R_2	R_4	R_6	R_1	Mol. Weight	M+H
610	Isoamyl	4-HO-phenyl	Methyl	Phenyl	466	467
611	Isoamyl	4-HO-phenyl	Methyl	4-Me-phenyl	480	481
612	Isoamyl	4-HO-phenyl	Methyl	3,5-Me_2-phenyl	494	495
613	Isoamyl	4-HO-phenyl	Methyl	4-MeO-phenyl	496	497
614	Isoamyl	4-HO-phenyl	Methyl	4-CF_3-phenyl	534	535
615	Isoamyl	4-HO-phenyl	Methyl	Cyclohexyl	472	473
616	Isoamyl	4-HO-phenyl	Methyl	Benzyl	480	481
617	Isoamyl	4-HO-phenyl	Methyl		494	495
618	Isoamyl	4-HO-phenyl	Methyl	4-MeO-benzyl	510	511
619	Isoamyl	4-HO-phenyl	Methyl	Phenethyl	494	495
620	Isoamyl	4-HO-phenyl	Methyl	Pentyl	460	461
621	Isoamyl	4-HO-phenyl	Methyl	Hexyl	474	475
622	Benzyl	4-HO-phenyl	Methyl	Phenyl	486	487
623	Benzyl	4-HO-phenyl	Methyl	4-Me-phenyl	500	501
624	Benzyl	4-HO-phenyl	Methyl	3,5-Me_2-phenyl	514	515
625	Benzyl	4-HO-phenyl	Methyl	4-MeO-phenyl	516	517

626	Benzyl	4-HO-phenyl	Methyl	4-CF_3-phenyl	554	555
627	Benzyl	4-HO-phenyl	Methyl	Cyclohexyl	492	493
628	Benzyl	4-HO-phenyl	Methyl	Benzyl	500	501
629	Benzyl	4-HO-phenyl	Methyl		514	515
630	Benzyl	4-HO-phenyl	Methyl	4-MeO-benzyl	530	531
631	Benzyl	4-HO-phenyl	Methyl	Phenethyl	514	515
632	Benzyl	4-HO-phenyl	Methyl	Pentyl	480	481
633	Benzyl	4-HO-phenyl	Methyl	Hexyl	494	495
634	Naphth-1-ylmethyl	4-HO-phenyl	Methyl	Phenyl	536	537
635	Naphth-1-ylmethyl	4-HO-phenyl	Methyl	4-Me-phenyl	550	551
636	Naphth-1-ylmethyl	4-HO-phenyl	Methyl	3,5-Me_2-phenyl	564	565
637	Naphth-1-ylmethyl	4-HO-phenyl	Methyl	4-MeO-phenyl	566	567
638	Naphth-1-ylmethyl	4-HO-phenyl	Methyl	4-CF_3-phenyl	604	605
639	Naphth-1-ylmethyl	4-HO-phenyl	Methyl	Cyclohexyl	542	543
640	Naphth-1-ylmethyl	4-HO-phenyl	Methyl	Benzyl	550	551
641	Naphth-1-ylmethyl	4-HO-phenyl	Methyl		564	565
642	Naphth-1-ylmethyl	4-HO-phenyl	Methyl	4-MeO-benzyl	580	581
643	Naphth-1-ylmethyl	4-HO-phenyl	Methyl	Phenethyl	564	565
644	Naphth-1-ylmethyl	4-HO-phenyl	Methyl	Pentyl	530	531
645	Naphth-1-ylmethyl	4-HO-phenyl	Methyl	Hexyl	544	545
646	Cyclohexylmethyl	4-HO-phenyl	Methyl	Phenyl	492	493
647	Cyclohexylmethyl	4-HO-phenyl	Methyl	4-Me-phenyl	506	507
648	Cyclohexylmethyl	4-HO-phenyl	Methyl	3,5-Me_2-phenyl	520	521
649	Cyclohexylmethyl	4-HO-phenyl	Methyl	4-MeO-phenyl	522	523
650	Cyclohexylmethyl	4-HO-phenyl	Methyl	4-CF_3-phenyl	560	561
651	Cyclohexylmethyl	4-HO-phenyl	Methyl	Cyclohexyl	468	469
652	Cyclohexylmethyl	4-HO-phenyl	Methyl	Benzyl	506	507
653	Cyclohexylmethyl	4-HO-phenyl	Methyl		520	521
654	Cyclohexylmethyl	4-HO-phenyl	Methyl	4-MeO-benzyl	536	537
655	Cyclohexylmethyl	4-HO-phenyl	Methyl	Phenethyl	520	521
656	Cyclohexylmethyl	4-HO-phenyl	Methyl	Pentyl	486	487
657	Cyclohexylmethyl	4-HO-phenyl	Methyl	Hexyl	500	501
658	4-methylbenzyl	4-HO-phenyl	Methyl	Phenyl	500	501
659	4-methylbenzyl	4-HO-phenyl	Methyl	4-Me-phenyl	514	515
660	4-methylbenzyl	4-HO-phenyl	Methyl	3,5-Me_2-phenyl	528	529
661	4-methylbenzyl	4-HO-phenyl	Methyl	4-MeO-phenyl	530	531
662	4-methylbenzyl	4-HO-phenyl	Methyl	4-CF_3-phenyl	568	569
663	4-methylbenzyl	4-HO-phenyl	Methyl	Cyclohexyl	506	507
664	4-methylbenzyl	4-HO-phenyl	Methyl	Benzyl	514	515
665	4-methylbenzyl	4-HO-phenyl	Methyl		528	529
666	4-methylbenzyl	4-HO-phenyl	Methyl	4-MeO-benzyl	544	545
667	4-methylbenzyl	4-HO-phenyl	Methyl	Phenethyl	528	529
668	4-methylbenzyl	4-HO-phenyl	Methyl	Pentyl	494	495
669	4-methylbenzyl	4-HO-phenyl	Methyl	Hexyl	508	509
670	Methoxypropyl	4-HO-phenyl	Methyl	Phenyl	468	469
671	Methoxypropyl	4-HO-phenyl	Methyl	4-Me-phenyl	482	483
672	Methoxypropyl	4-HO-phenyl	Methyl	3,5-Me_2-phenyl	496	497
673	Methoxypropyl	4-HO-phenyl	Methyl	4-MeO-phenyl	498	499
674	Methoxypropyl	4-HO-phenyl	Methyl	4-CF_3-phenyl	536	537
675	Methoxypropyl	4-HO-phenyl	Methyl	Cyclohexyl	474	475

676	Methoxypropyl	4-HO-phenyl	Methyl	Benzyl	482	483
677	Methoxypropyl	4-HO-phenyl	Methyl		496	497
678	Methoxypropyl	4-HO-phenyl	Methyl	4-MeO-benzyl	512	513
679	Methoxypropyl	4-HO-phenyl	Methyl	Phenethyl	496	497
680	Methoxypropyl	4-HO-phenyl	Methyl	Pentyl	462	463
681	Methoxypropyl	4-HO-phenyl	Methyl	Hexyl	476	477
682	Phenethyl	4-HO-phenyl	Methyl	Phenyl	500	501
683	Phenethyl	4-HO-phenyl	Methyl	4-Me-phenyl	514	515
684	Phenethyl	4-HO-phenyl	Methyl	3,5-Me_2-phenyl	528	529
685	Phenethyl	4-HO-phenyl	Methyl	4-MeO-phenyl	530	531
686	Phenethyl	4-HO-phenyl	Methyl	4-CF_3-phenyl	568	569
687	Phenethyl	4-HO-phenyl	Methyl	Cyclohexyl	506	507
688	Phenethyl	4-HO-phenyl	Methyl	Benzyl	514	515
689	Phenethyl	4-HO-phenyl	Methyl		528	529
690	Phenethyl	4-HO-phenyl	Methyl	4-MeO-benzyl	544	545
691	Phenethyl	4-HO-phenyl	Methyl	Phenethyl	528	529
692	Phenethyl	4-HO-phenyl	Methyl	Pentyl	494	495
693	Phenethyl	4-HO-phenyl	Methyl	Hexyl	508	509
694	2,2-bisphenylethyl	4-HO-phenyl	Methyl	Phenyl	576	577
695	2,2-bisphenylethyl	4-HO-phenyl	Methyl	4-Me-phenyl	590	591
696	2,2-bisphenylethyl	4-HO-phenyl	Methyl	3,5-Me_2-phenyl	604	605
697	2,2-bisphenylethyl	4-HO-phenyl	Methyl	4-MeO-phenyl	606	607
698	2,2-bisphenylethyl	4-HO-phenyl	Methyl	4-CF_3-phenyl	644	645
699	2,2-bisphenylethyl	4-HO-phenyl	Methyl	Cyclohexyl	582	583
700	2,2-bisphenylethyl	4-HO-phenyl	Methyl	Benzyl	586	587
701	2,2-bisphenylethyl	4-HO-phenyl	Methyl		604	605
702	2,2-bisphenylethyl	4-HO-phenyl	Methyl	4-MeO-benzyl	620	621
703	2,2-bisphenylethyl	4-HO-phenyl	Methyl	Phenethyl	604	605
704	2,2-bisphenylethyl	4-HO-phenyl	Methyl	Pentyl	570	571
705	2,2-bisphenylethyl	4-HO-phenyl	Methyl	Hexyl	584	585
706	Naphth-1-ylmethyl	Benzyl	Methyl	Phenyl	520	521
707	Naphth-1-ylmethyl	Benzyl	Methyl	4-Me-phenyl	534	535
708	Naphth-1-ylmethyl	Benzyl	Methyl	3,5-Me_2-phenyl	548	549
709	Naphth-1-ylmethyl	Benzyl	Methyl	4-MeO-phenyl	550	551
710	Naphth-1-ylmethyl	Benzyl	Methyl	4-CF_3-phenyl	588	589
711	Naphth-1-ylmethyl	Benzyl	Methyl	Cyclohexyl	526	527
712	Naphth-1-ylmethyl	Benzyl	Methyl	Benzyl	534	535
713	Naphth-1-ylmethyl	Benzyl	Methyl		548	549
714	Naphth-1-ylmethyl	Benzyl	Methyl	4-MeO-benzyl	564	565
715	Naphth-1-ylmethyl	Benzyl	Methyl	Phenethyl	548	549
716	Naphth-1-ylmethyl	Benzyl	Methyl	Pentyl	514	515
717	Naphth-1-ylmethyl	Benzyl	Methyl	Hexyl	528	529
718	Naphth-1-ylmethyl	 spiro	Methyl	Phenyl	498	499
719	Naphth-1-ylmethyl	 spiro	Methyl	4-Me-phenyl	512	513

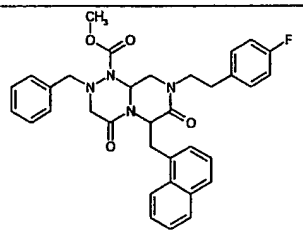
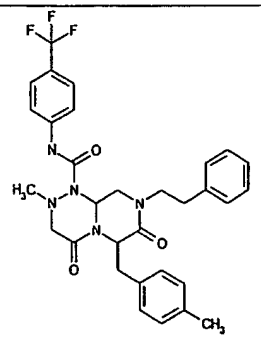
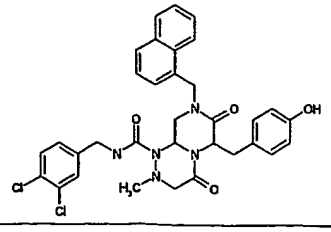
720	Naphth-1-ylmethyl		Methyl	3,5-Me_2-phenyl	526	527
721	Naphth-1-ylmethyl		Methyl	4-MeO-phenyl	528	529
722	Naphth-1-ylmethyl		Methyl	4-CF_3-phenyl	566	567
723	Naphth-1-ylmethyl		Methyl	Cyclohexyl	504	505
724	Naphth-1-ylmethyl		Methyl	Benzyl	512	513
725	Naphth-1-ylmethyl		Methyl		526	527
726	Naphth-1-ylmethyl		Methyl	4-MeO-benzyl	542	543
727	Naphth-1-ylmethyl		Methyl	Phenethyl	526	527
728	Naphth-1-ylmethyl		Methyl	Pentyl	492	493
729	Naphth-1-ylmethyl		Methyl	Hexyl	506	507
730	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl	Phenyl	570	571
731	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl	4-Me-phenyl	584	585
732	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl	3,5-Me_2-phenyl	598	599
733	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl	4-MeO-phenyl	600	601
734	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl	4-CF_3-phenyl	638	639
735	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl	Cyclohexyl	576	577
736	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl	Benzyl	584	585
737	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl		598	599
738	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl	4-MeO-benzyl	614	615
739	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl	Phenethyl	598	599
740	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl	Pentyl	564	565
741	Naphth-1-ylmethyl	Naphth-1-ylmethyl	Methyl	Hexyl	578	579
742	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl	Phenyl	526	527
743	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl	4-Me-phenyl	540	541
744	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl	3,5-Me_2-phenyl	554	555
745	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl	4-MeO-phenyl	556	557
746	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl	4-CF_3-phenyl	594	595
747	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl	Cyclohexyl	532	533
748	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl	Benzyl	540	541
749	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl		554	555
750	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl	4-MeO-benzyl	570	571
751	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl	Phenethyl	554	555
752	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl	Pentyl	520	521

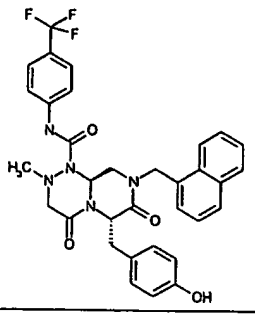
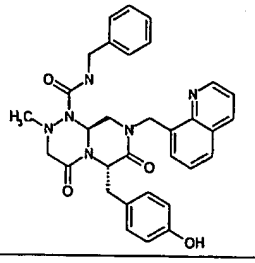
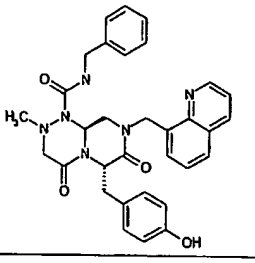
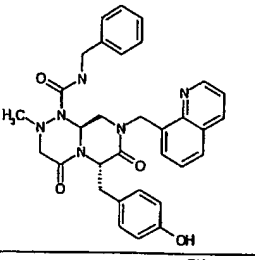
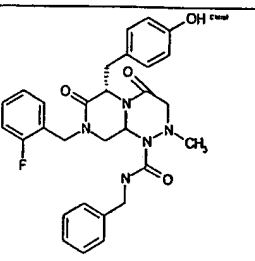
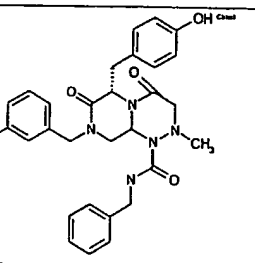
753	Naphth-1-ylmethyl	Cyclohexylmethyl	Methyl	Hexyl	534	535
754	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl	Phenyl	554	555
755	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl	4-Me-phenyl	568	569
756	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl	3,5-Me_2-phenyl	582	583
757	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl	4-MeO-phenyl	584	585
758	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl	4-CF_3-phenyl	622	623
759	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl	Cyclohexyl	560	561
760	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl	Benzyl	568	569
761	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl		582	583
762	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl	4-MeO-benzyl	598	599
763	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl	Phenethyl	582	583
764	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl	Pentyl	548	549
765	Naphth-1-ylmethyl	4-chlorobenzyl	Methyl	Hexyl	562	563
766	Naphth-1-ylmethyl	Methyl	Methyl	Phenyl	444	445
767	Naphth-1-ylmethyl	Methyl	Methyl	4-Me-phenyl	458	459
768	Naphth-1-ylmethyl	Methyl	Methyl	3,5-Me_2-phenyl	472	473
769	Naphth-1-ylmethyl	Methyl	Methyl	4-MeO-phenyl	474	475
770	Naphth-1-ylmethyl	Methyl	Methyl	4-CF_3-phenyl	512	513
771	Naphth-1-ylmethyl	Methyl	Methyl	Cyclohexyl	450	451
772	Naphth-1-ylmethyl	Methyl	Methyl	Benzyl	458	459
773	Naphth-1-ylmethyl	Methyl	Methyl		472	473
774	Naphth-1-ylmethyl	Methyl	Methyl	4-MeO-benzyl	488	489
775	Naphth-1-ylmethyl	Methyl	Methyl	Phenethyl	472	473
776	Naphth-1-ylmethyl	Methyl	Methyl	Pentyl	438	439
777	Naphth-1-ylmethyl	Methyl	Methyl	Hexyl	452	453
778	Naphth-1-ylmethyl	Isobutyl	Methyl	Phenyl	486	487
779	Naphth-1-ylmethyl	Isobutyl	Methyl	4-Me-phenyl	500	501
780	Naphth-1-ylmethyl	Isobutyl	Methyl	3,5-Me_2-phenyl	514	515
781	Naphth-1-ylmethyl	Isobutyl	Methyl	4-MeO-phenyl	516	517
782	Naphth-1-ylmethyl	Isobutyl	Methyl	4-CF_3-phenyl	554	555
783	Naphth-1-ylmethyl	Isobutyl	Methyl	Cyclohexyl	492	493
784	Naphth-1-ylmethyl	Isobutyl	Methyl	Benzyl	500	501
785	Naphth-1-ylmethyl	Isobutyl	Methyl		514	515
786	Naphth-1-ylmethyl	Isobutyl	Methyl	4-MeO-benzyl	530	531
787	Naphth-1-ylmethyl	Isobutyl	Methyl	Phenethyl	514	515
788	Naphth-1-ylmethyl	Isobutyl	Methyl	Pentyl	480	481
789	Naphth-1-ylmethyl	Isobutyl	Methyl	Hexyl	494	495
790	Naphth-1-ylmethyl	Methylthioethyl	Methyl	Phenyl	504	505
791	Naphth-1-ylmethyl	Methylthioethyl	Methyl	4-Me-phenyl	518	519
792	Naphth-1-ylmethyl	Methylthioethyl	Methyl	3,5-Me_2-phenyl	532	533
793	Naphth-1-ylmethyl	Methylthioethyl	Methyl	4-MeO-phenyl	534	535
794	Naphth-1-ylmethyl	Methylthioethyl	Methyl	4-CF_3-phenyl	572	573
795	Naphth-1-ylmethyl	Methylthioethyl	Methyl	Cyclohexyl	510	511
796	Naphth-1-ylmethyl	Methylthioethyl	Methyl	Benzyl	518	519
797	Naphth-1-ylmethyl	Methylthioethyl	Methyl		532	533
798	Naphth-1-ylmethyl	Methylthioethyl	Methyl	4-MeO-benzyl	548	549
799	Naphth-1-ylmethyl	Methylthioethyl	Methyl	Phenethyl	532	533
800	Naphth-1-ylmethyl	Methylthioethyl	Methyl	Pentyl	498	499
801	Naphth-1-ylmethyl	Methylthioethyl	Methyl	Hexyl	512	513

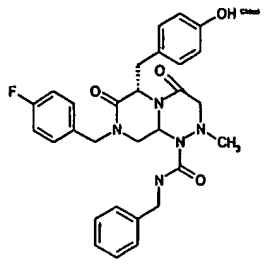
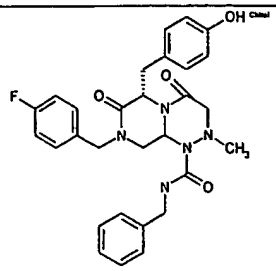
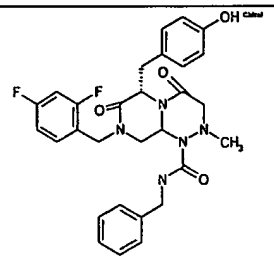
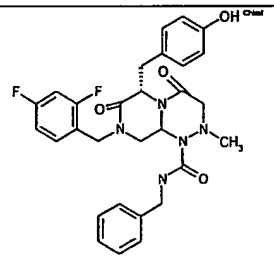
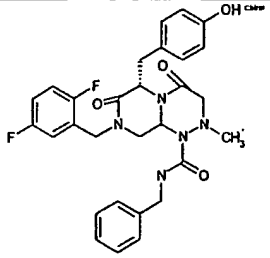
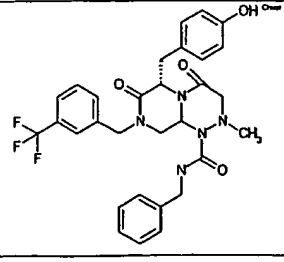
In a further aspect of this invention, methods for screening the libraries for bioactivity and isolating bioactive library members are disclosed. The libraries of the present invention were screened for bioactivity by various techniques and methods. In general, the screening assay may be performed by (1) contacting the mimetics of a library with a biological target of interest, such as a receptor, to allow binding between the mimetics of the library and the target to occur, and (2) detecting the binding event by an appropriate assay, such as the calorimetric assay disclosed by Lam et al. (*Nature* 354:82-84, 1991) or Griminski et al. (*Biotechnology* 12:1008-1011, 1994) (both of which are incorporated herein by reference). In a preferred embodiment, the library members are in solution and the target is immobilized on a solid phase. Alternatively, the library may be immobilized on a solid phase and may be probed by contacting it with the target in solution.

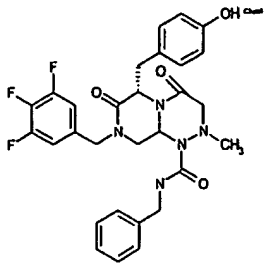
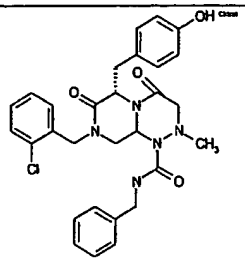
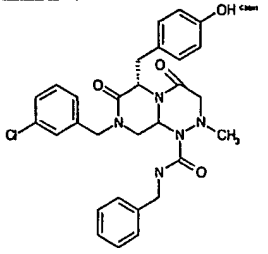
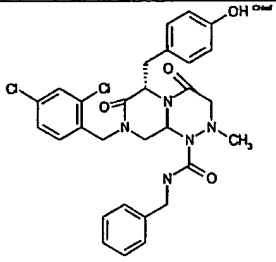
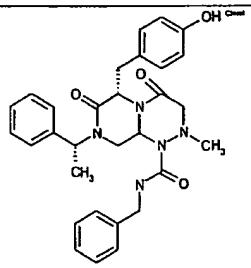
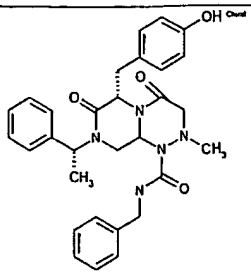
Table 4 below shows compounds for bioactivity test selected from the library of the present invention and IC_{50} values thereof, which are measured by the Reporter gene assay as described in Example 6.

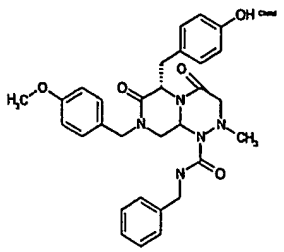
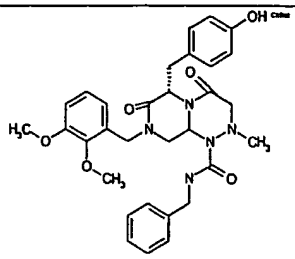
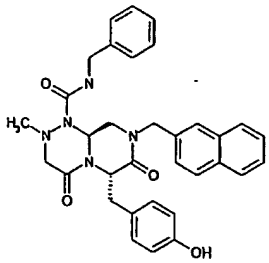
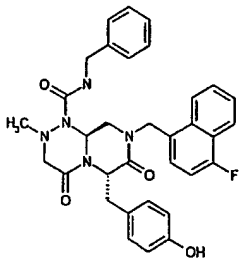
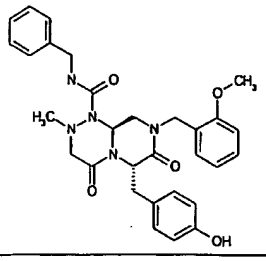
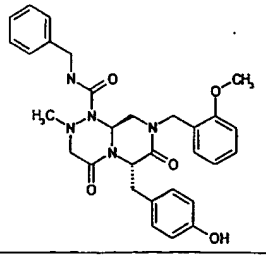
[Table 4] $IC_{50}(\mu M)$ of Selected Library Compounds

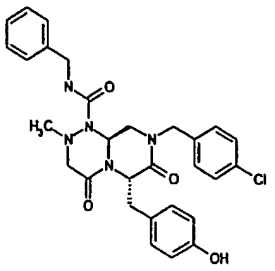
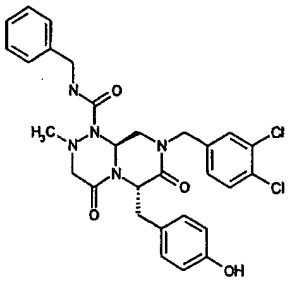
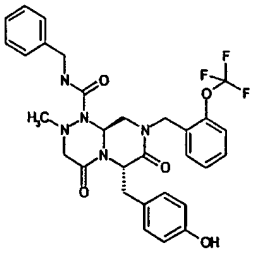
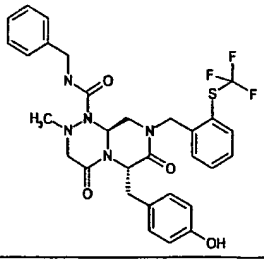
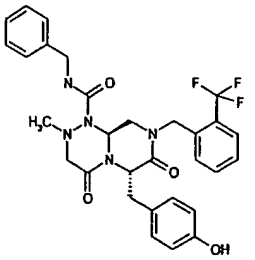
No	STRUCTURE	M.W.	$IC_{50}(\mu M)$
1		580.7	12.8
2		579.6	12.6
3		632.5	13.9

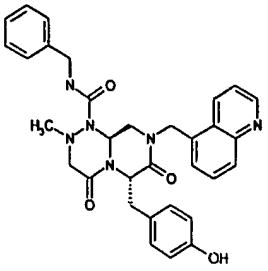
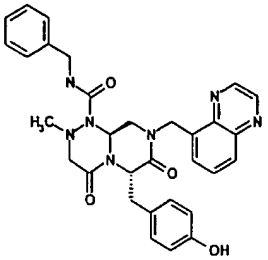
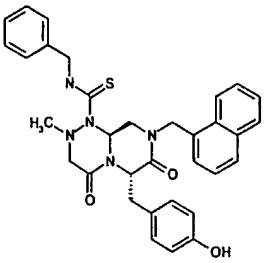
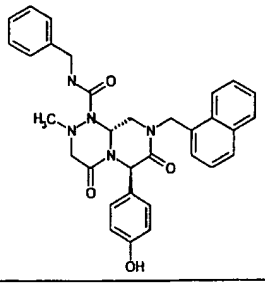
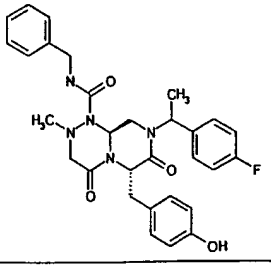
4		617.6	11.8
5		564.6	6.8
6		564.6	6.1
7		564.6	2.2
8		531.6	14.5
9		531.6	6.7

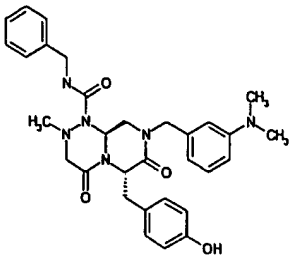
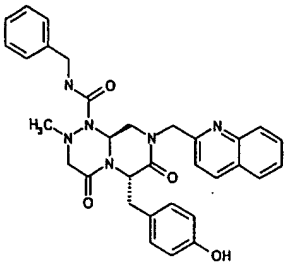
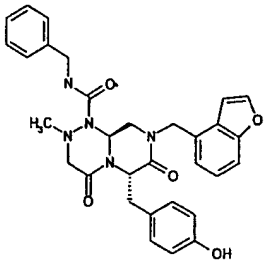
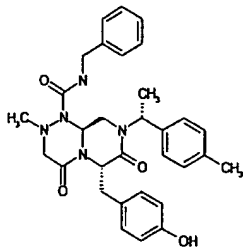
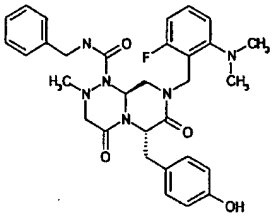
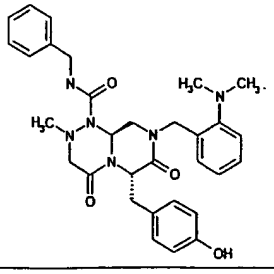
10		531.6	4.0
11		531.6	4.6
12		549.6	9.0
13		549.6	6.4
14		549.6	17.7
15		581.6	4.2

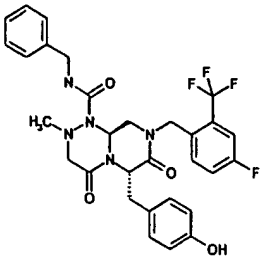
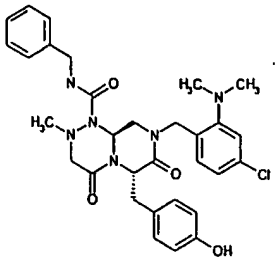
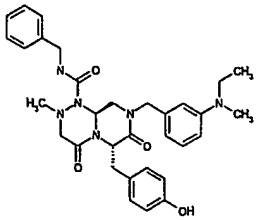
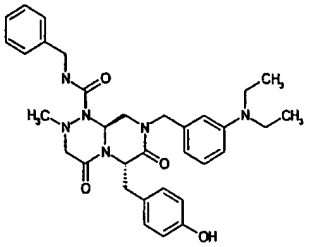
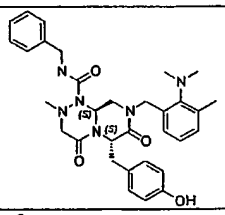
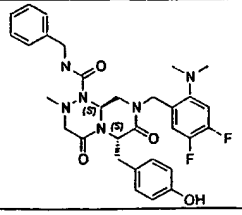
16		567.6	3.8
17		548.0	14.3
18		548.0	3.3
19		582.5	11.5
20		527.6	5.1
21		527.6	5.0

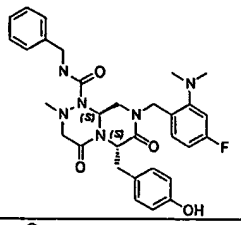
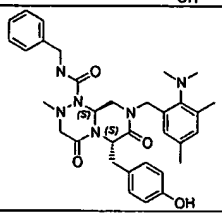
22		543.6	10.4
23		573.6	10.7
24		563.7	5.0
25		581.6	3.0
26		543.6	7.1
27		543.6	5.2

28		548.0	7.5
29		582.5	3.8
30		597.6	7.5
31		613.7	11.9
32		581.6	4.1

33		564.6	13.0
34		565.6	4.4
35		579.7	11.4
36		549.6	12.5
37		545.6	2.3

38		556.7	7.1
39		564.6	9.7
40		553.6	7.0
41		541.6	13.6
42		574.7	18.2
43		556.7	5.2

44		599.6	1.3
45		591.1	2.2
46		570.7	4.4
47		584.7	3.5
48		570.7	10.9
49		592.6	1.4

50		574.6	1.3
51		584.7	4.8

It is found in the present invention that the compound of general formula (I), especially the compound of general formula (VI) can inhibit CBP-mediated transcriptional activation in cancer cells due to its specific binding to CBP, and it is supported by immunoprecipitation of CBP of SW480 cells with the compound of the present invention.

The compound of the present invention can also inhibit the survivin expression in SW480 cells, and therefore, inhibit the oncogenic activity in cancer cells. The compound of the present invention can be used for inhibiting cancer cells, and thus, would be useful for the regulation of cell growth. Supporting such results, the compound of the present invention further shows that it can induce the caspase-3 activation in SW480 cells, and therefore, induce the apoptotic activity in cells. The compound of the present invention can be also advantageously used for inducing apoptosis in cells.

To confirm the oncogenic activity in cancer cell in invitro MTS cytotoxicity assay was tested by following method.

Cytotoxicity test

SW480 or HCT116 cells were placed into 96 well microplate (10^4cells/well) and incubated for 24 hours at 37 °C. The cells were treated with TCF4 compound at various concentrations for 24 hours. 20 μl of MTS solution (Promega) was added into each well and incubated for 2 hours at 37 °C. Cell viability was measured by reading the absorbance at 490nm using microplate reader (Molecular Device) and cytotoxicity of a compound at each concentration was calculated.

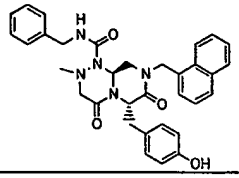
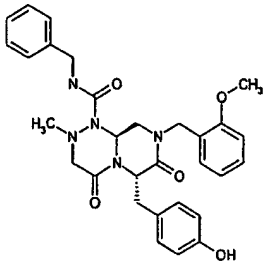
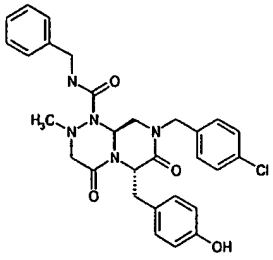
Growth Inhibition assay

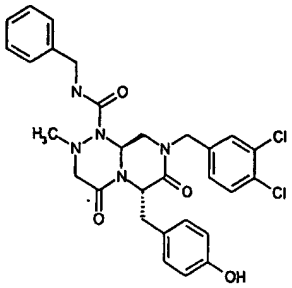
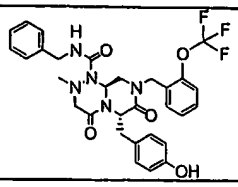
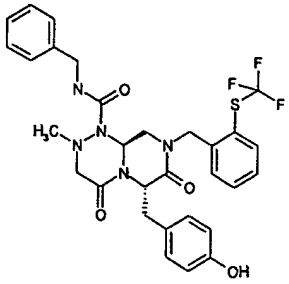
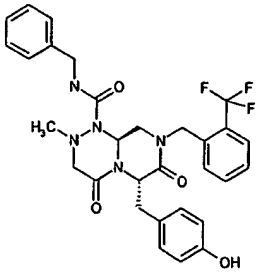
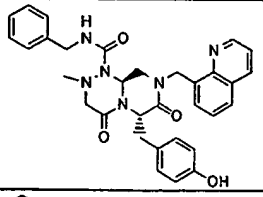
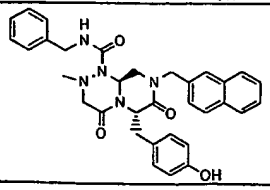
SW480 or HCT116 cells were placed into 96 well microplate (10^4cells/well) and incubated for 24 hours at 37 °C. 20 μl of [3-(4,5-dimethylthiazol-2-yl)-5-(3-

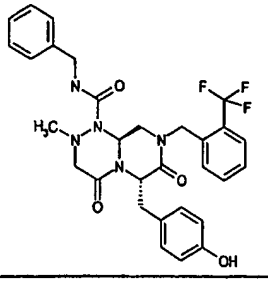
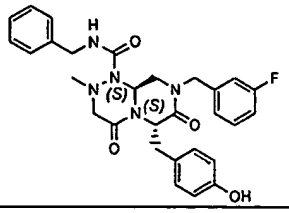
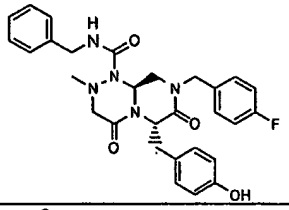
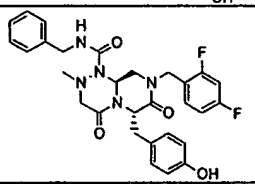
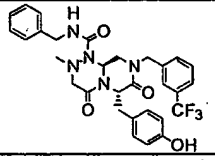
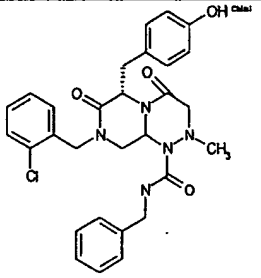
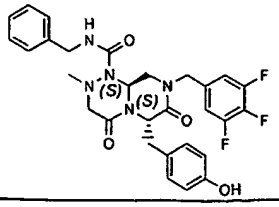
carboxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt](MTS) solution (Promega) was added into each well and the absorbance after 2 hour incubation at 37 °C (negative control) was read. And then, the cells were treated with TCF4 compound at various concentrations for 48 hours. 20 μl of MTS solution (Promega) was added into each well and incubated for 2 hour at 37 °C. Cell viability was measured by reading the absorbance at 490nm using a microplate reader (Molecular device) and cytotoxicity of a compound at each concentration was calculated.

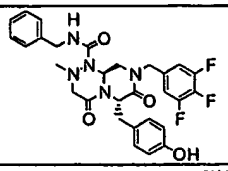
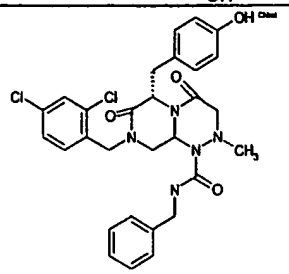
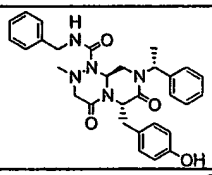
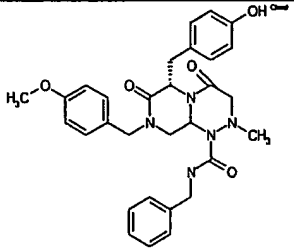
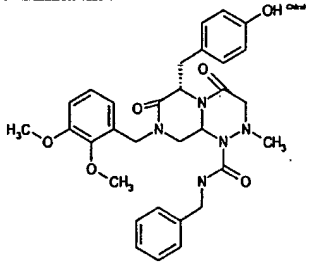
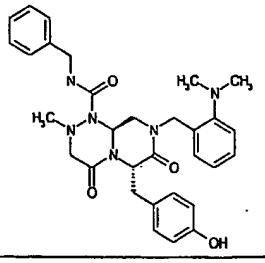
The results of oncogenic activity for selected library compounds were shown in the Table 5.

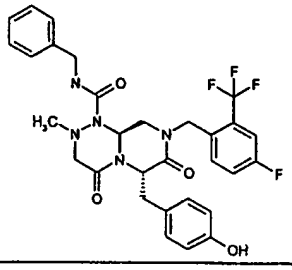
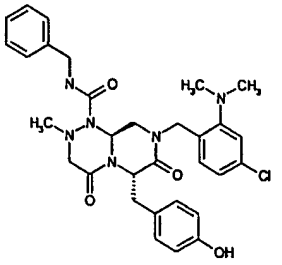
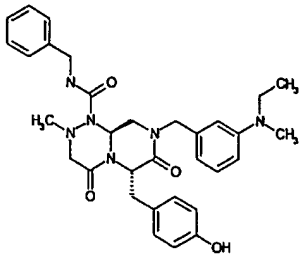
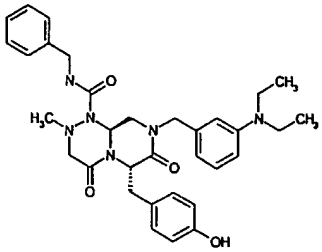
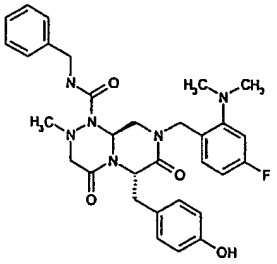
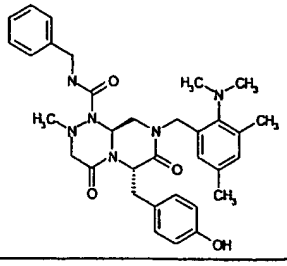
[Table 5] Oncogenic Activity by MTS or Sulforhodamine B assay for Selected Library Compounds

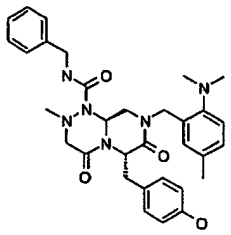
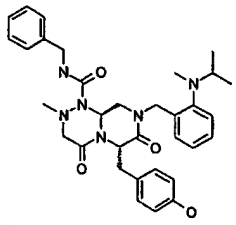
Compound	Structure	Growth Inhibition (GI50, uM)	
		SW480	HCT116
1		2.28	1.78
2		2.58	2.23
3		2.73	2.39

4		1.99	1.91
5		2.32	2.06
6		3.96	3.91
7		1.22	0.73
8		<0.3	<0.3
9		2.36	1.92

10		2.34	1.66
11		1.97	1.30
12		2.54	1.48
13		1.65	1.59
14		2.70	2.10
15		1.68	1.34
16		4.18	2.95

17		1.12	0.74
18		4.63	3.52
19		2.66	1.17
20		5.02	2.75
21		5.25	1.67
22		6.58	3.26

23		3.9	25.41
24		13.79	1.67
25		24.53	1.81
26		23.89	3.06
27		11.7	1.13
28		3.57	5.47

29		15.98	7.93
30		14.05	5.4

In another aspect of the present invention, a pharmaceutical composition containing the compound having the general formula (I), especially the compound of general formula (VI) is disclosed. For the preparation of the pharmaceutical composition containing the present compounds, a skilled person in the art can use publicly known knowledge and techniques which are known in the pertinent art. Generally known varieties of carriers and other additives are used for the preparation of the composition of the present invention. The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that is desired to be treated, for example by oral, rectal or parenteral administration.

For these purposes, the compounds of the present invention may be formulated by means known in the art into a form of, for example, tablets, capsules, aqueous or oily solutions or suspension, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of the present invention is one suitable for oral administration in unit dosage form such as, for example a tablet or capsule which contains from about 1mg to about 1g of the compound of this invention.

In another aspect, a pharmaceutical composition of the present invention is one suitable for intravenous, subcutaneous or intramuscular injection. A patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of about 1 ug/kg to about 1g/kg of the compound of the present invention. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time.

Alternatively a patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following table illustrates representative pharmaceutical dosage forms containing the compound or pharmaceutically-acceptable salt thereof for therapeutics or prophylactic use in humans :

Tablet 1	mg/tablet
Compound	100
Lactose Ph. Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

Tablet 2	mg/tablet
Compound	50
Lactose Ph. Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

Tablet 3	mg/tablet
Compound	1.0
Lactose Ph. Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

Capsule	mg/capsule
Compound	10
Lactose Ph. Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.0

Injection I	(50mg/ml)
Compound	0.5% w/v
Isotonic aqueous solution	to 100%

The pharmaceutical composition containing the compound of general formula (I), especially the compound of general formula (VI) can be used for treatment of disorders modulated by Wnt signaling pathway, especially cancer, more especially colorectal cancer.

In another aspect of the present invention, a method for inhibiting the growth of tumor cell in a subject in which the method comprises administering to a tumor cell a safe and effective amount of the compounds of the present invention is disclosed. The composition containing such compounds also can be used for the inhibition of tumor cells.

Thus, this method can be useful to treat cancer in a mammalian subject. It can be advantageously used for treating colorectal cancer.

In another aspect of the present invention, a method for treating a disorder modulated by Wnt signaling pathway in which the method comprises administering to a patient a safe and effective amount of the compounds having general formula (I), especially the compound of general formula (VI) is disclosed. Pharmaceutical composition containing the compound of the present invention can be also used for this purpose. In this connection, it is found in the present invention that the compounds having general formula (I), especially the compound of general formula (VI) or the pharmaceutical composition containing thereof can be useful for the treatment of disorder modulated by TCF4 - β catenin – CBP complex, which is believed to be responsible for initiating the overexpression of cancer cells related to Wnt signaling pathway. Thus, it is another aspect of the present invention to provide a method for the treatment of disorder modulated by TCF4 - β catenin – CBP complex, using the compounds having the general formula (I), especially the compound of general formula (VI).

Further, because the treatment of cancer is also closely related to inducing apoptosis in cancer cells in a subject, the present invention is also directed to a method of inducing apoptosis in cancer cells using the compounds of general formula (I), especially the compound of general formula (VI).

It has been known from previous art that 5-FU [Fluorouracil; 5-fluoro-2,4(1H, 3H)-pyrimidinedione] can induce apoptosis in cultured oral cancer cells (D. Tong et al., Oral Oncology 36, 2000 236-241). Further, it is also known that colon cancer has a sensitivity to 5-FU (D. Arango et al., Cancer Research 61, 2001 4910-4915). In the present invention, therefore, the combination of 5-FU having established anti-cancer activity and the compounds of formula (I), especially the compound of general formula (VI) of the present invention is prepared and tested against SW480 cell lines. As a result, it is found that the combination of 5-FU with the compounds of the present invention, especially TCF4 compound, has a remarkable effect for inhibiting cancer cell growth such as SW480 cells.

Therefore, it is yet another aspect of the present invention to provide a method of treating cancer, which comprises administering to a subject a safe and effective amounts of the compound having formula (I) of Claim 1, especially the compound of general formula (VI), together with other anti-cancer agent such as 5-Fu.

Compounds of the present invention have been shown to inhibit the expression of survivin. Blanc-Brude *et al.*, *Nat. Medicine* 8:987 (2002), have shown that survivin is a critical regulator of smooth muscle cell apoptosis which is important in pathological

vessel-wall remodeling. Accordingly, another aspect of the present invention provides a method of treating or preventing restenosis associated with angioplasty comprising administering to a subject in need thereof a safe and effective amount of a reverse-turn mimetic of the present invention. In one embodiment the invention treats the restenosis, *i.e.*, administration of a reverse-turn mimetic of the present invention to a subject having restenosis achieves a reduction in the severity, extent, or degree, etc. of the restenosis. In another embodiment the invention prevents the restenosis, *i.e.*, administration of a reverse-turn mimetic of the present invention to a subject that is anticipated to develop new or additional restenosis achieves a reduction in the anticipated severity, extent, or degree, etc. of the restenosis. Optionally, the subject is a mammalian subject.

Compounds of the present invention have been shown to inhibit TCF/B-catenin transcription. Rodova *et al.*, *J. Biol. Chem.* 277:29577 (2002), have shown that PKD-1 promoter is a target of the B-catenin/TCF pathway. Accordingly, another aspect of the present invention provides a method of treating or preventing polycystic kidney disease comprising administering to a subject in need thereof a safe and effective amount of a reverse-turn mimetic of the present invention. In one embodiment the invention treats the polycystic kidney disease, *i.e.*, administration of a reverse-turn mimetic of the present invention to a subject having polycystic kidney disease achieves a reduction in the severity, extent, or degree, etc. of the polycystic kidney disease. In another embodiment the invention prevents polycystic kidney disease, *i.e.*, administration of a reverse-turn mimetic of the present invention to a subject that is anticipated to develop new or additional polycystic kidney disease achieves a reduction in the anticipated severity, extent, or degree, etc. of the polycystic kidney disease. Optionally, the subject is a mammalian subject.

Compounds of the present invention have been shown to inhibit the expression of Wnt signaling. Hanai *et al.*, *J. Cell Bio.* 158:529 (2002), have shown that endostatin, a known anti-angiogenic factor, inhibits Wnt signaling. Accordingly, another aspect of the present invention provides a method of treating or preventing aberrant angiogenesis disease comprising administering to a subject in need thereof a safe and effective amount of a reverse-turn mimetic of the present invention. In one embodiment the invention treats the aberrant angiogenesis disease, *i.e.*, administration of a reverse-turn mimetic of the present invention to a subject having aberrant angiogenesis disease achieves a reduction in the severity, extent, or degree, etc. of the aberrant angiogenesis disease. In another embodiment the invention prevents aberrant angiogenesis disease, *i.e.*, administration of a reverse-turn mimetic of the present invention to a subject that is anticipated to develop new or additional aberrant angiogenesis disease achieves a reduction

in the anticipated severity, extent, or degree, etc. of the aberrant angiogenesis disease. Optionally, the subject is a mammalian subject.

Compounds of the present invention have been shown to inhibit the expression of Wnt signalling. Sen *et al.*, *P.N.A.S. (USA)* 97:2791 (2000), have shown that mammals with rheumatoid arthritis demonstrate increased expression of Wnt and Fz in RA synovial tissue. Accordingly, another aspect of the present invention provides a method of treating or preventing rheumatoid arthritis disease comprising administering to a subject in need thereof a safe and effective amount of a reverse-turn mimetic of the present invention. In one embodiment the invention treats the rheumatoid arthritis disease, *i.e.*, administration of a reverse-turn mimetic of the present invention to a subject having rheumatoid arthritis disease achieves a reduction in the severity, extent, or degree, etc. of the rheumatoid arthritis disease. In another embodiment the invention prevents rheumatoid arthritis disease, *i.e.*, administration of a reverse-turn mimetic of the present invention to a subject that is anticipated to develop new or additional rheumatoid arthritis disease achieves a reduction in the anticipated severity, extent, or degree, etc. of the rheumatoid arthritis disease. Optionally, the subject is a mammalian subject.

Compounds of the present invention have been shown to inhibit the expression of Wnt signalling. Uthoff *et al.*, *Int. J. Oncol.* 19:803 (2001), have shown that differential upregulation of disheveled and fz (Wnt pathway molecules) occurs in ulcerative colitis (compared to Chron's disease patients). Accordingly, another aspect of the present invention provides a method of treating or preventing ulcerative colitis comprising administering to a subject in need thereof a safe and effective amount of a reverse-turn mimetic the present invention. In one embodiment the invention treats the ulcerative colitis, *i.e.*, administration of a reverse-turn mimetic of the present invention to a subject having ulcerative colitis achieves a reduction in the severity, extent, or degree, etc. of the ulcerative colitis. In another embodiment the invention prevents ulcerative colitis, *i.e.*, administration of a reverse-turn mimetic of the present invention to a subject that is anticipated to develop new or additional ulcerative colitis achieves a reduction in the anticipated severity, extent, or degree, etc. of the ulcerative colitis. Optionally, the subject is a mammalian subject.

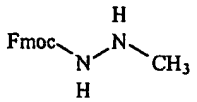
BEST MODE CARRYING OUT THE INVENTION

The following non-limiting examples illustrate the compound, composition, and methods of use of this invention.

EXAMPLES

Preparation Example 1 : Preparation of (*N*-Fmoc-*N'*-R_3-hydrazino)-acetic acid

(1) Preparation of *N*-Fmoc-*N'*-Methyl Hydrazine

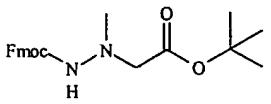


2 L, two-neck, round-bottomed-flask was fitted with a glass stopper and a calcium tube. A solution of methylhydrazine sulfate (20 g, 139 mmol) in THF (300 mL) was added and a solution of DiBoc (33 g, 153 mmol) in THF was added. Saturated sodium bicarbonate aqueous solution (500mL) was added dropwise via addition funnel over 2 hours with vigorous stirring. After 6 hours, A solution of Fmoc-Cl (39 g, 153 mmol) in THF was added slowly. Resulting suspension was stirred for 6 hours at 0 °C. The mixture was extracted with EA (500 mL) and the organic layer was retained. The solution was dried with sodium sulfate and evaporated *in vacuo*. The next step was proceeded without purification.

1 L, two-necked, round-bottom-flask was fitted with a glass stopper and a calcium tube. A solution of reaction mixture in MeOH (300mL) was added and a conc. HCl (30 mL, 12 N) was added slowly via addition funnel with magnetic stirring in ice water bath and stirred overnight. The mixture was extracted with EA (1000 mL) and the organic layer was retained. The solution was dried with sodium sulfate and evaporated *in vacuo*. The residue was purified crystallization with n-hexane and EA to give product (32.2 g, 83 %).

^{1}HNMR (DMSO-D6) δ 7.90~7.88 (d, *J*=6 Hz, 2H,), δ 7.73~7.70 (d, *J*=9 Hz, 2H,), 7.44~7.31 (m, 4H), 4.52~4.50 (d, *J*=6 Hz, 2H), 4.31~4.26 (t, *J*=6 Hz, 1H), 2.69 (s, 1H)

(2) Preparation of (*N*-Fmoc-*N'*-methyl-hydrazino)-acetic acid t-butyl ester

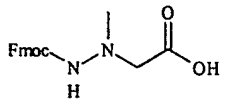


1 L, two-necked, round-bottom-flask was fitted with a glass stopper and reflux condenser connected to a calcium tube. A solution of *N*-Fmoc-*N'*-Methyl-Hydrazine (20 g, 75 mmol) in toluene (300 mL) was added. A solution of t-butylbromo acetate (22 g, 111 mmol) in toluene (50mL) was added slowly. Cs_2CO_3 (49 g, 149 mmol) was added

slowly. NaI (11 g, 74 mmol) was added slowly with vigorous stirring. The reaction mixture was stirred at reflux temperature over 1 day. A mixture was filtered and extracted the organic layer with ethyl acetate[EA] (500 mL). The solution was dried with sodium sulfate and evaporated *in vacuo*. The product was purified by chromatography with haxane : EA = 2 : 1 solution to give product (19.8 g, 70 %).

^{1}H-NMR ($CDCl_3$-d) δ 7.78~7.75 (d, *J*=9 Hz, 2H,), δ 7.61~7.59 (d, *J*=6 Hz, 2H,), 7.43~7.26 (m, 4H), 4.42~4.40 (d, *J*=6 Hz, 2H), 4.23 (b, 1H), 3.57 (s, 2H), 2.78 (s, 3H), 1.50 (s, 9H)

(3) Preparation of (*N*-Fmoc-*N'*-methyl-hydrazino)-acetic acid

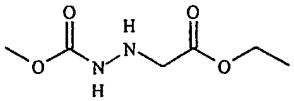


1 L, two-neck, round-bottomed-flask was fitted with a glass stopper and reflux condenser connected to a calcium tube. (*N*-Fmoc-*N'*-methyl-hydrazino)-acetic acid t-butyl ester (20 g, 52 mmol) was added. A solution of HCl (150 mL, 4 M solution in dioxane) was added slowly with vigorous stirring in an ice water bath. The reaction mixture was stirred at RT over 1 day. The solution was concentrated completely under reduced pressure at 40 °C. The saturated aq. $NaHCO_3$ solution (100 mL) was added and the aqueous layer was washed with diethyl ether (100 mL). The conc. HCl was dropwised slowly at 0 °C (pH 2-3). The mixture was extracted and the organic layer was retained (500 mL, MC). The solution was dried with sodium sulfate and evaporated *in vacuo*. The residue was purified by recrystallization with n-hexane and ethyl acetate to give product (12 g, 72 %).

^{1}H-NMR (DMSO-d_6) δ 12.38 (s, 1H), 8.56 (b, 1H), 7.89~7.86 (d, *J*=9 Hz, 2H,), δ 7.70~7.67 (d, *J*=9 Hz, 2H,), 7.43~7.29 (m, 4H), 4.29~4.27 (d, *J*=6 Hz, 2H), 4.25~4.20 (t, *J*=6 Hz, 1H), 3.47 (s, 2H), 2.56 (s, 3H)

Preparation Example 2 : Preparation of (*N*-Moc-*N'*-R_7-hydrazino)-acetic acid

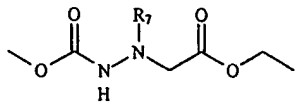
(1) Preparation of (*N'*-Methoxycarbonyl-hydrazino)-acetic acid ethyl ester



The methyl carbazate (50g, 0.55mol) was dissolved in DMF (300ml), and then ethyl bromoacetate (68ml, 0.555mol), potassium carbonate (77g, 0.555mol) were added to the reaction vessel. The mixture was warmed to 50°C for 5hours. After the reaction was completed, the mixture was filtered, and diluted with EtOAc, and washed with brine

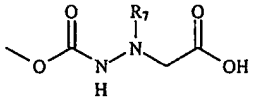
(3 times). The crude product was purified by column (eluent : Hex/EtOAc = 4/1).
Pdt : 72g (colorless oil)

(2) [*N*-R_7-*N'*-methoxycarbonyl-hydrazino]-acetic acid ethyl ester



The ethyl ester (10g, 0.05 mol) , potassium carbonate (6.9g, 0.05mol), and R_3-bromide (14.1g, 0.06mol) were dissolved in DMF (200ml), and The mixture was warmed to 50°C for 5hours. After the reaction was completed, the mixture was filtered, and diluted with EA, and washed with brine (3 times). The crude product was purified by Chromatography (eluent : Hex/EtOAc = 4/1).

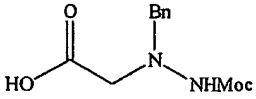
(3) [*N*-R_7-*N'*-methoxycarbonyl-hydrazino]-acetic acid



The alkylated ethyl ester (9.5g, 0.03mol) was dissolved in THF/water (1/1, ml), and added 2N NaOH (28.3ml) solution at 0 °C. The mixture was stirred at RT for 2 hours. After the starting ester was not detected on UV, the solution was diluted with EA, then separated. The aqueous layer was acidified to pH 3~4 by 1N HCl, and the compound was extracted by DCM (3 times). The combined organic layer was dried over MgSO4, and evaporated to give a yellow solid.

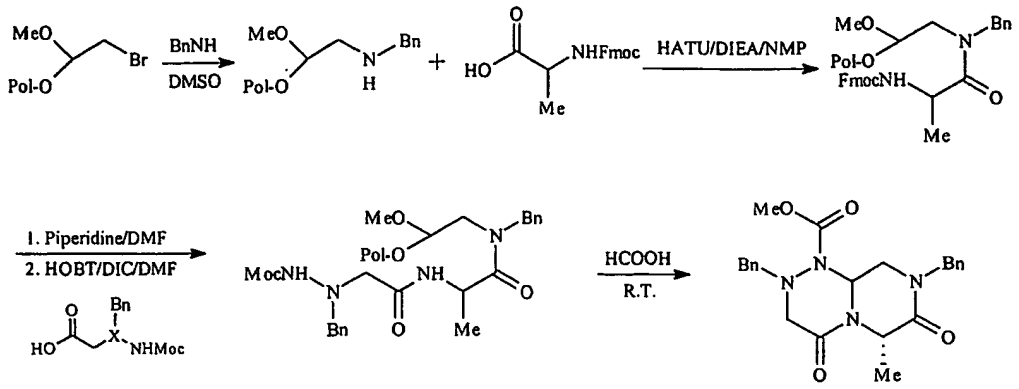
EXAMPLE 1

(1) Preparation of N^{β}-Moc-N^{α}-benzyl-hydrazinoglycine



This compound was prepared according to literature procedure. (Cheguillaume et. al., *Synlett* 2000, 3, 331)

(2) Preparation of 1-Methoxycarbonyl-2,8-dibenzyl-6-methyl-4,7-dioxo-hexahydro-pyrazino[2,1-c][1,2,4]triazine



The bromoacetal resin (60 mg, 0.98 mmol/g) and a solution of benzyl amine in DMSO (2.5 ml, 2 M) were placed in vial with screw cap. The reaction mixture was shaken at 60 °C using rotating oven [Robbins Scientific] for 12 hours. The resin was collected by filtration, and washed with DMF, then DCM.

A solution of Fmoc-alanine (4 equiv.), HATU [PerSeptive Biosystems] (4 equiv.), and DIEA (4 equiv.) in NMP (Advanced ChemTech) was added to the resin. After the reaction mixture was shaken for 4 hours at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

To the resin was added 20% piperidine in DMF. After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

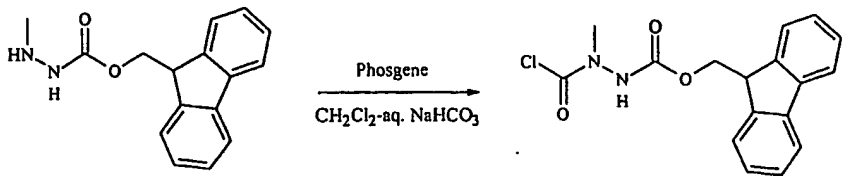
A solution of N^{β}-Moc-N^{α}-benzyl-hydrazinoglycine (4 equiv.), HOBT [Advanced ChemTech] (4 equiv.), and DIC (4 equiv.) in DMF was added to the resin prepared above. After the reaction mixture was shaken for 3 hours at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then MeOH. The resin was dried *in vacuo* at room temperature

The resin was treated with formic acid (2.5 ml) for 18 hours at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure to give the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm; 1.51 (d, 3H), 2.99 (m, 1H), 3.39 (d, 1H), 3.69 (m, 1H), 3.75 (m, 1H), 3.82 (s, 3H), 4.02 (d, 1H), 4.24 (d, 1H), 4.39 (d, 1H), 4.75 (d, 1H), 5.14 (q, 1H), 5.58 (dd, 1H), 7.10-7.38 (m, 10H).

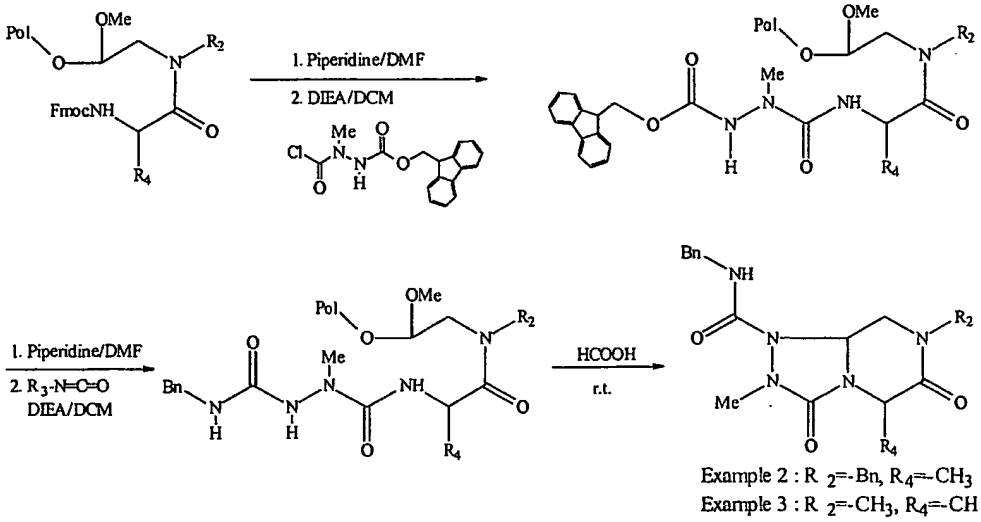
EXAMPLE 2

(1) Preparation of *N'*-Fmoc-*N*-methyl-hydrazinocarbonyl chloride



An ice-cooled biphasic mixture of N-Methyl hydrazine carboxylic acid 9H-Fluoren-9-ylmethyl ester (107 mg, 0.4 mmol) in 15 ml of CH_2Cl_2 and 15 ml of saturated aq. $NaHCO_3$ was rapidly stirred while a 1.93 M phosgene in toluene (1.03 ml, 2 mmol) was added as a single portion. The reaction mixture was stirred for 30 min, the organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 128 mg (97 %) of carbamoyl chloride as a foamy solid. [Caution: Phosgene vapor is highly toxic. Use it in a hood] This product was used for the following solid phase synthesis without further purification.

(2) Preparation of 2,5-Dimethyl-7-benzyl-3,6-dioxo-hexahydro-[1,2,4]triazolo[4,5-a]pyrazine-1-carboxylic acid benzylamide



Example 2 : R_2=-Bn, R_4=-CH_3
Example 3 : R_2=-CH_3, R_4=-CH

The bromoacetal resin (30 mg, 0.98 mmol/g) and a solution of benzyl amine in DMSO (1.5 ml, 2 M) were placed in vial with screw cap. The reaction mixture was shaken at 60 °C using rotating oven [Robbins Scientific] for 12 hours. The resin was collected by filtration, and washed with DMF, then DCM.

A solution of Fmoc-alanine (3 equiv.), HATU [PerSeptive Biosystems] (3 equiv.), and DIEA (3 equiv.) in NMP (Advanced ChemTech) was added to the resin. After the reaction mixture was shaken for 4 hours at room temperature, the resin was collected by

filtration and washed with DMF, DCM, and then DMF.

To the resin was added 20% piperidine in DMF. After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

A solution of *N'*-Fmoc-*N*-methyl-hydrazinocarbonyl chloride (5 equiv.) obtained in the above step (1), DIEA (5 equiv.) in DCM was added to the resin prepared above. After the reaction mixture was shaken for 4 hours at room temperature, the resin was collected by filtration and washed with DMF, DCM, and DMF.

To the resin was added 20% piperidine in DMF (10 ml for 1 g of the resin). After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

The resin was treated with a mixture of benzyl isocyanate (4 equiv.) and DIEA (4 equiv.) in DCM for 4 hours at room temperature. Then, the resin was collected by filteration and washed with DMF, DCM, and then MeOH. The resin was dried *in vacuo* at room temperature.

The resin was treated with formic acid for 14 hours at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure to give the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm; 1.48 (d, 3H), 2.98 (s, 3H), 3.18 (m, 1H), 3.46 (m, 1H), 4.37-4.74 (m, 5H), 5.66 (dd, 1H), 6.18 (m, 1H), 7.10-7.40 (m, 10H).

EXAMPLE 3

Preparation of 2,5,7-Trimethyl-3,6-dioxo-hexahydro-[1,2,4]triazolo[4,5-a]pyrazine-1-carboxylic acid benzylamide

The title compound is prepared according to the same procedure with Example 2.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm; 1.48 (d, 3H), 2.99 (s, 3H), 3.03 (s, 3H), 3.38 (m, 1H), 3.53 (dd, 1H), 4.36 (dd, 1H), 4.52 (q, 1H), 4.59 (dd, 1H), 5.72 (dd, 1H), 6.19 (br.t, 1H), 7.10-7.38 (m, 5H).

EXAMPLE 4

Preparation of 2-Methyl-5-(*p*-hydroxyphenylmethyl)-7-naphthylmethyl-3,6-dioxo-hexahydro-[1,2,4]triazolo[4,5-a]pyrazine-1-carboxylic acid benzylamide

The bromoacetal resin (30 mg, 0.98 mmol/g) and a solution of naphthylmethyl amine in DMSO (1.5 ml, 2 M) were placed in vial with screw cap. The reaction mixture was shaken at 60 °C using rotating oven [Robbins Scientific] for 12 hours. The resin was collected by filtration, and washed with DMF, then DCM.

A solution of Fmoc-Tyr(OBut)-OH (3 equiv.), HATU [PerSeptive Biosystems] (3

equiv.), and DIEA (3 equiv.) in NMP (Advanced ChemTech) was added to the resin. After the reaction mixture was shaken for 4 hours at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

To the resin was added 20% piperidine in DMF. After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

A solution of *N*'-Fmoc-*N*-methyl-hydrazinocarbonyl chloride (5 equiv.), DIEA (5 equiv.) in DCM was added to the resin prepared above. After the reaction mixture was shaken for 4 hours at room temperature, the resin was collected by filtration and washed with DMF, DCM, and DMF.

To the resin was added 20% piperidine in DMF (10 ml for 1 g of the resin). After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

The resin was treated with a mixture of benzyl isocyanate (4 equiv.) and DIEA (4 equiv.) in DCM for 4 hours at room temperature. Then, the resin was collected by filteration and washed with DMF, DCM, and then MeOH. The resin was dried *in vacuo* at room temperature.

The resin was treated with formic acid for 14 hours at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure to give the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm; 2.80-2.98 (m, 5H), 3.21-3.37 (m, 2H), 4.22-4.52 (m, 2H), 4.59 (t, 1H), 4.71 (d, 1H), 5.02 (dd, 1H), 5.35 (d, 1H), 5.51 (d, 1H), 6.66 (t, 2H), 6.94 (dd, 2H), 7.21-8.21 (m, 12H).

EXAMPLE 5

Preparation of 2-Methyl-6-(*p*-hydroxyphenylmethyl)-8-naphthyl-4,7-dioxo-hexahydro-pyrazino[2,1-c][1,2,4]triazine-1-carboxylic acid benzylamide

The bromoacetal resin (60 mg, 0.98 mmol/g) and a solution of naphthyl amine in DMSO (2.5 ml, 2 M) were placed in vial with screw cap. The reaction mixture was shaken at 60 °C using rotating oven [Robbins Scientific] for 12 hours. The resin was collected by filtration, and washed with DMF, then DCM.

A solution of Fmoc- Tyr(OBut)-OH (4 equiv.), HATU [PerSeptive Biosystems] (4 equiv.), and DIEA (4 equiv.) in NMP (Advanced ChemTech) was added to the resin. After the reaction mixture was shaken for 4 hours at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

To the resin was added 20% piperidine in DMF. After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed

with DMF, DCM, and then DMF.

A solution of N^{β}-Fmoc-N^{α}-benzyl-hyrazinoglycine (4 equiv.), HOBT [Advanced ChemTech] (4 equiv.), and DIC (4 equiv.) in DMF was added to the resin prepared above. After the reaction mixture was shaken for 3 hours at room temperature, the resin was collected by filtration and washed with DMF, and then DCM. To the resin was added 20% piperidine in DMF (10 ml for 1 g of the resin). After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

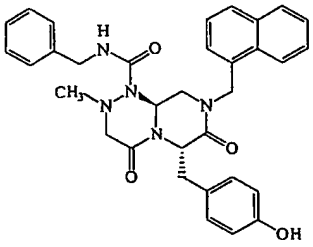
The resin was treated with a mixture of benzyl isocyanate (4 equiv.) and DIEA (4 equiv.) in DCM for 4 hours at room temperature. Then, the resin was collected by filteration and washed with DMF, DCM, and then MeOH. After the resin was dried *in vacuo* at room temperatur, the resin was treated with formic acid (2.5 ml) for 18 hours at room temperature. The resin was removed by filtration, and the filtrate was condensed under reduced pressure to give the product as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm; 2.73 (s, 3H), 3.13 (d, 1H), 3.21-3.38 (m, 3H), 3.55 (d, 1H), 3.75 (t, 1H), 4.22 (dd, 1H), 4.36 (dd, 1H), 4.79 (d, 1H), 5.22 (t, 1H), 5.47 (m, 2H), 6.68 (d, 2H), 6.99 (d, 2H), 7.21-8.21 (m, 12H);
MS (m/z, ESI) 564.1 (MH^+) 586.3 (MNa^+).

EXAMPLE 6

Bioassay for the measurement of IC_{50} against SW480 cells and Cytotoxicity test on the cell lines were proceeded by following methods:

Test compound has been prepared in the Example 4



Reporter Gene Assay

SW480 cells were transfected with the usage of Superfect™ transfect reagent (Qiagen, 301307). Cells were trypsinized briefly 1 day before transfection and plated on 6 well plate (5 x 10^5 cells/well) so that they were 50-80% confluent on the day of transfection.

Four microgram (TOPFlash) and one microgram (pRL-null) of DNAs were diluted in 150 μl of serum-free medium, and 30 μl of Superfect™ transfect reagent was

added. The DNA-Superfect mixture was incubated at room temperature for 15 min, and then, 1 ml of 10 % FBS DMEM was added to this complex for an additional 3 hours of incubation. While complexes were forming, cells were washed with PBS twice without antibiotics.

The DNA-Superfect™ transfect reagent complexes were applied to the cells before incubating at 37 °C at 5 % CO_2 for 3 hours. After incubation, recovery medium with 10 % FBS was added to bring the final volume to 1.18 ml. After 3 hours incubation, the cells were harvested and reseeded to 96 well plate (3 x 10^4 cells/well). After overnight incubation at 37 °C at 5 % CO_2, the cells were treated with the test compound for 24 hours. Finally, the activity was checked by means of luciferase assay (Promega, E1960).

Fig. 1 illustrates the results of the measurement of IC_{50} of the above compound for SW480 cells.

Sulforhodamine B (SRB) assay

Growth inhibitory effect of the above compound on the cells listed below was measured by the sulforhodamine B assay. SW480 cells in 100 μl media were plated in each well of 96-well plate and allowed to attach for 24 hours. Compound was added to the wells to produce the desired final concentrations, and the plates were incubated at 37 °C for 48 hours. The cells were then fixed by gentle addition of 100 μl of cold (4 °C) 10% trichloroacetic acid to each well, followed by incubation at 4 °C for 1 hour. Plates were washed with deionized water five times and allowed to air dry. The cells were then stained by addition of 100 μl SRB solution (0.4% SRB(w/v) in 1% acetic acid (v/v)) to wells for 15 min. After staining, the plates were quickly washed five times with 1% acetic acid to remove any unbound dye, and allowed to air dry. Bound dye was solubilized with 10 mmol/L Tris base (pH 10.5) prior to reading the plates. The optical density (OD) was read on a plate reader at a wavelength of 515nm with Molecular Device. Inhibition of growth was expressed as relative viability (% of control) and GI_{50} was calculated from concentration-response curves after log/probit transformation.

[Table 6] In vitro cyctotoxicity (SRB) assay of the compound obtained in Example 4

Origin	Cell	Example 4	Cisplatin	5-FU
Colon	T84	1.134	> 10	1.816
	LOVO	0.532	> 10	1.029
	HT29	1.694	> 10	5.334
	DLD-1	1.775	> 10	> 10
	COLO205	1.136	> 10	1.130

	CACO-2	1.201	> 10	0.451
	SW480-Kribb	1.137	> 10	> 10
	SW480-CWP	0.980	4.502	> 10
	SW620	1.426	> 10	5.570
	KM12	1.451	> 10	2.729
	HCT15	2.042	> 10	1.179
	HCT116	0.96	> 10	1.039
	HCC2998	1.047	> 10	5.486
	786-0	1.417	3.347	0.584
Leukemia	HL60	1.243	> 10	7.010
	RPMI8226	1.1.177	> 10	> 10
	K562/VIN	1.640	> 10	7.071
	K562/ADR	7.682	> 10	> 10
	K562	1.247	> 10	6.133
Prostate	PC3	1.207	> 10	> 10
	HT1080	1.469	> 10	0.798
Lung	A549	1.386	> 10	1.007
	NCI H460	1.498	> 10	1.397
	NCI H23	1.296	5.176	2.254
Renal	293	0.731	6.641	2.015
	CAKI-1	0.467	> 10	0.925
	ACHN	1.263	5.019	5.062
Melanoma	RPMI7951	0.936	5.010	0.920
	M14	2.289	3.447	1.225
	HMV-II	4.834	3.190	0.695
	HMV-I	1.153	5.478	2.110
	G361	0.584	4.827	1.539
	CRL1579	1.830	0.699	> 10
	A431	1.083	3.722	0.404
	A253	1.398	2.084	2.926
	UACC62	0.563	> 10	1.093
	SK-MEL-28	1.291	> 10	> 10
	SK-MEL-5	0.888	> 10	2.434
	LOX-IMVI	1.526	> 10	> 10
	A375	1.391	> 10	1.464
Breast	MCF7/ADR	9.487	9.907	> 10
	MCF7	7.355	> 10	1.751

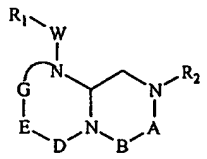
It will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except by the appended claims.

INDUSTRIAL APPLICABILITY

The compounds of the invention which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins, can inhibit the expression of survivin, TCF/B-catenin transcription, and the expression of Wnt signaling. Therefore, the present invention can provide a pharmaceutical composition and/or a method for inhibiting the growth of tumor cell in a mammalian subject, for treating cancer in combination with other anti-neoplastic agents, for treating or preventing diseases such as restenosis associated with angioplasty, polycystic kidney disease, aberrant angiogenesis disease, rheumatoid arthritis disease and ulcerative colitis, as well as a method of identifying a biologically active compound, and a library of compounds.

We claim:

1. A compound having the following general formula (I):



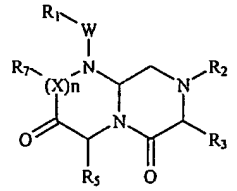
(I)

wherein A is -(CHR_3)- or -(C=O)-, B is -(CHR_4)-, -(C=O)-, D is –(CHR_5)- or –(C=O)-, E is –(ZR_6)-, -(C=O)-, G is –(XR_7)$_n$-, -(CHR_7)-(NR_8)-, -(C=O)-(XR_9)-, or -(C=O)- , W is –Y(C=O)-, -(C=O)NH-, -(SO_2)- or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers thereof.

2. The compound of claim 1, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and $R_9$are independently selected from the group consisting of aminoC_{2-5}alkyl, guanidinoC_{2-5}alkyl, C_{1-4}alkylguanidinoC_{2-5}alkyl, diC_{1-4}alkylguanidino-C_{2-5}alkyl, amidinoC_{2-5}alkyl,C_{1-4}alkylamidinoC_{2-5}alkyl, diC_{1-4}alkylamidinoC_{2-5}alkyl, C_{1-3}alkoxy, Phenyl, substituted phenyl(where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), naphthyl, substituted naphthyl(where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl(where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridyl, substituted pyridyl, (where the substituents are independently selected from one or more of amino amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridylC_{1-4}alkyl, substituted pyridylC_{1-4}alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-}

$_4$alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyrimidylC_{1-4}alkyl, substituted pyrimidylC_{1-4}alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy or nitro, carboxy, cyano, sulfuryl or hydroxyl), triazin-2-yl-C_{1-4}alkyl, substituted triazin-2-yl-C_{1-4}alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), imidazoC_{1-4}alkyl, substituted imidazol C_{1-4}alkl (where the imidazole sustituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), imidazolinylC_{1-4}alkyl, N-amidinopiperazinyl-N-C_{0-4}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, C_{1-5}dialkylaminoC_{2-5}alkyl, N-amidinopiperidinylC_{1-4}alkyl and 4-aminocyclohexylC_{0-2}alkyl;

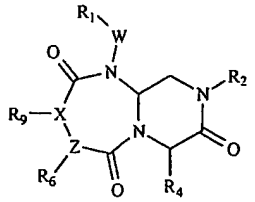
3. The compound of claim 1 wherein A is –(CHR_3)-, B is –(C=O)-, D is –(CHR_5)-, E is –(C=O)-, G is –(XR_7)$_n$-, and the compound has the following general formula (II):



(II)

wherein R_1, R_2, R_3, R_5, R_7, W, X and n are as defined in claim 1.

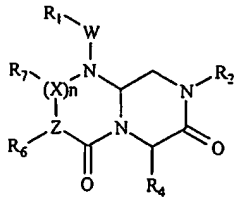
4. The compound of claim 1 wherein A is –(C=O)-, B is -(CHR_4) -, D is –(C=O)-, E is –(ZR_6)-, G is –(C=O)-(XR_9)-, and the compound has the following general formula (III):



(III)

wherein R_1, R_2, R_4, R_6, R_9, W and X are as defined in claim 1, Z is nitrogen or CH (when Z is CH, then X is nitrogen).

5. The compound of claim 1 wherein A is –(C=O)-, B is –(CHR_4)-, D is –(C=O)-, E is –(ZR_6)-, G is $(XR_7)_n$-, and the compound has the following general formula (IV):



(IV)

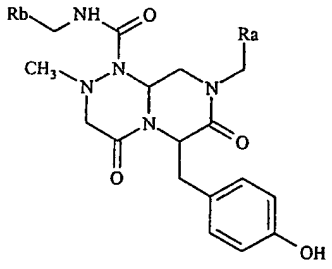
wherein R_1, R_2, R_4, R_6, R_7, W, X and n are as defined in claim 1, and Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero).

6. The compound of any one of claims 2, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 or R_9 is joined to a solid support or solid support derivatives.

7. The compound of any one of claims 3, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 or R_9 is joined to a solid support or solid support derivatives.

8. The compound of any one of claims 4, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 or R_9 is joined to a solid support or solid support derivatives.

9. The compound of claim 5, wherein the compound has the following general formula (VI):



(VI)

wherein, R_a is a bicyclic aryl group having 8 to 11 ring members, which may have 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur, and R_b is a monocyclic aryl group having 5 to 7 ring members, which may have 1 to 2 heteroatoms selected from nitrogen, oxygen or sulfur, and aryl ring in the compound may have one or more substituents selected from a group consisting of halide, hydroxy, cyano, lower alkyl, and lower alkoxy group.

10. The compound of claim 9, wherein R_a is naphthyl, quinolinyl or isoquinolinyl group, and R_b is phenyl, pyridyl or piperidyl, all of which may be substituted with one or more substituents selected from a group consisting of halide, hydroxy, cyano, lower alkyl, and lower alkoxy group.

11. The compound of claim 9, wherein R_a is naphthyl, and R_b is phenyl, which may be substituted with one or more substituents selected from a group consisting of halide, hydroxy, cyano, lower alkyl, and lower alkoxy group.

12. A library of compounds, comprising at least one compound of any one of claims i through 9.

13. A pharmaceutical composition comprising a compound of claim 1 and pharmaceutically acceptable carrier.

14. The pharmaceutical composition according to Claim 13, in which the composition comprises a safe and effective amount of the compound of Claim 9 and a pharmaceutically acceptable carrier.

15. A method for inhibiting the growth of tumor cell in a mammalian subject, the method comprising administering to a tumor cell a safe and effective amount of the composition of any one of Claim 1, 3, 4 and 5.

16. A method for inhibiting the growth of tumor cell in a mammalian subject, the method comprising administering to a tumor cell a safe and effective amount of the composition of Claim 9.

17. A method according to Claim 15 or 16, in which the tumor cell is colorectal cells.

18. A method of treating cancer comprising administering to a subject a safe and effective amounts of the compound having formula (I) of Claim 1,3,4,5,9 in combination with other anti-neoplastic agents such as 5-FU, taxol, cisplatin, mitomycin C, tegafur, raltitrexed, capecitabine, and irinotecan, etc.

19. A method of treating or preventing restenosis associated with angioplasty comprising administering to a subject in need thereof a safe and effective amount of a

compound of any one of claims 1, 3, 4, 5 or 9.

20. A method of treating or preventing polycystic kidney disease comprising administering to a subject in need thereof a safe and effective amount of a compound of any one of claims 1, 3, 4, 5 or 9.

21. A method of treating or preventing aberrant angiogenesis disease comprising administering to a subject in need thereof a safe and effective amount of a compound of any one of claims 1, 3, 4, 5 or 9.

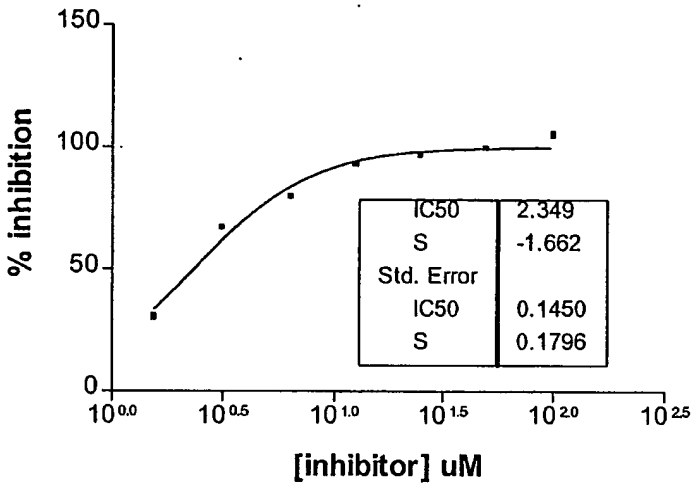
22. A method of treating or preventing rheumatoid arthritis disease comprising administering to a subject in need thereof a safe and effective amount of a compound of any one of claims 1, 3, 4, 5 or 9.

23. A method of treating or preventing ulcerative colitis comprising administering to a subject in need thereof a safe and effective amount of a compound of any one of claims 1, 3, 4, 5 or 9.

24. A method of identifying a biologically active compound, comprising contacting the library of claim 12 with a target to detect or screen the biologically active compound

Figure 1

H-101651



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 02/01901

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 487/04; A61K 31/53, 31/4985;

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT patent documents

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY and CAPLUS Databases, STN International; WPI Database, DErwent Publications Ltd., EPO PAJ Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/00210 A1 (MOLECUMETICS LTD.) 4 January 2001 (04.01.01) ; *the whole document.*	9-11,13,14
A	WO 97/15577 A1 (MOLECUMETICS LTD.) 1 May 1997 (01.05.97) ; *the whole document.*	9-11,13,14
A	M. EGUCHI et al., "Solid-phase synthesis and solution structure of bicyclic ß-turn peptidomimetics: diversity at the i position", Tetrahedron Letters 42, 2001, pages 1237-1239; *the whole document.*	9-11,13,14
A	WO 98/49168 A1 (MOLECUMIMETICS LTD.) 5 November 1998 (05.11.98) ; *the whole document.*	9-11,13,14

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2003 (13.01.2003)	28 January 2003 (28.01.2003)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer WENIGER S. Telephone No. 1/53424/341

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 02/01901

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-8, 12 and 18-24
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see Supplemaental Sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

1. claims 1-8 relate to such a huge number of compounds being in theory defined by the broad generic formula (I), that a meaningful search is not possible. Furthermore, only a small part of those compounds a) finds support by the disclosure of the present application and b) for only a small part of those compounds an (pharmaceutical) effect has been illustrated. This small part of compounds is represented by the formula given in claim 9.

2. A library of compounds according to claim 12 represents an undefined, open set of chemical compounds and cannot be considered to be a subject matter which is defined or defineable in a clear and concise manner.

3. Claims 18-23 are directed to methods of treatment of the human or animal body by therapy. But these methods claimed are only speculative and therefore lack support of disclosure, because neither an effect or activity of the compounds of the present application which could show the suitability of of these compounds for treatments according to claims 19-23, nor a corresponding effect compounds of the present application in combination with further agents mentioned in claim 18 has been illustrated.

4. Claim 24 describes the general problem to be solved, only, not its technical solution.

REMARKS:

1. Although claim 15-17 are directed to a treatment of the human or animal body by therapy, the search has been carried out and based on the alleged effects of the composition.

2. There is a discrepancy between the name of the compound prepared in example 4 (a "triazolo-pyrazine compound" and page 19 of the description and example 6, resp.. According to page 19 and example 6 the compound prepared according to example 4 has to be a triazine-pyrazine!

In contrast example 5 could describe the preparation of a "triazolo-pyrazine" compound, but calls the product a "pyrazino-triazine" compound.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 02/01901-0

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
WO	A	0210				none	
WO	A1	9715577	01-05-1997	AT	E	203025	15-07-2001
				AU	A1	75205/96	15-05-1997
				AU	B2	719620	11-05-2000
				DE	C0	69613861	16-08-2001
				DE	T2	69613861	15-11-2001
				EP	A1	876371	11-11-1998
				EP	B1	876371	11-07-2001
				ES	T3	2158360	01-09-2001
				JP	T2	11513986	30-11-1999
				US	A	5929237	27-07-1999
				US	A	6013458	11-01-2000
				US	BA	6184223	06-02-2001
				US	AA	01039274	08-11-2001
				US	AA	02022620	21-02-2002
				US	BB	6413963	02-07-2002
				AU	A1	71679/98	24-11-1998
				AU	B2	743777	07-02-2002
				EP	A1	980373	23-02-2000
				JP	T2	01526651	18-12-2001
				WO	A1	9849168	05-11-1998
				AU	A5	00056300	31-01-2001
				EP	A1	1227813	07-08-2002
				WO	A1	00100210	04-01-2001
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				US	A	6013458	11-01-2000
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				AU	B2	719620	11-05-2000
				DE	C0	69613861	16-08-2001
				DE	T2	69613861	15-11-2001
				EP	A1	876371	11-11-1998
				EP	B1	876371	11-07-2001
				ES	T3	2158360	01-09-2001
				JP	T2	11513986	30-11-1999
				US	A	5929237	27-07-1999
				WO	A1	9715577	01-05-1997
				AU	A5	00056300	31-01-2001
				EP	A1	1227813	07-08-2002
				WO	A1	00100210	04-01-2001